Sub 26 – Submission regarding Transparency of the Therapeutic Goods Administration

From the Endocrine Society of Australia

Background:
Submissions have been invited from relevant professional bodies to comment on information provided by the TGA, including Consumer Medicine Information and Approved Product Information. This area is of particular relevance to Endocrinology Therapeutics with respect to thyroid and adrenal conditions. One of the prominent members of the ESA, life member Professor Jim Stockigt, has previously drawn attention to these issues in the form of a review article and editorial, both published in the Medical Journal of Australia [1, 2].

Current Issues:
It is of concern that errors of fact remain in the current versions of PI and CMI for several important endocrinological drugs. Approximately 5% of the Australian population take medication for thyroid disorders. These drugs have been widely available for decades, but new information becomes available which is slow to be incorporated into PI and CMI. For example, new information has become available in the last two years regarding hepatotoxicity for the drug propylthiouracil [3]. It is now considered to be contraindicated for use in children and adolescents [4], yet this information is not in the current PI (see attachment). While adrenal insufficiency (both primary and secondary) is less common, glucocorticoid dosing errors are highly likely to lead to significant morbidity and even death. Therefore the importance of accurate information for both prescribers and patients could not be overstated.

The intention of this submission is not to reiterate the points previously made in Professor Stockigt’s publications (attached), nor to perform a detailed review of individual PIs and CMIs. Associate Professor Warrick Inder from the Department of Endocrinology at St Vincent’s Hospital Melbourne undertook a comprehensive review and correction of PIs for two glucocorticoid medications commonly used to treat adrenal insufficiency – hydrocortisone (Hysone, Alphapharm) and cortisone acetate (Cortate, Aspen Pharmacare Australia Pty Ltd). Subsequent to this review, the suggested changes were adopted for the Hysone PI but completely ignored by Aspen Pharmacare for the Cortate PI.
Recommendations from the Endocrine Society of Australia:

The ESA would like to draw attention to the points previously raised by Professor Stockigt, with the relevant publications attached as Appendix 1

Specifically:

The TGA formulate a mechanism by which PI and CMI for all medications are reviewed on a regular basis. The frequency may need to be varied depending on the drug in question, and could range from annually to every 5 years.

This review should be performed by the Pharmaceutical Company in conjunction with appropriate clinical expertise which is readily available in Australia. This requires close liaison with the Specialty Colleges and Sub-Specialty societies as relevant to the particular area of therapeutics.

Any bureaucratic issues which limit this process must be revised.

A mechanism is developed whereby expert clinicians who discover sections of PI or CMI which are at odds with modern clinical practice and advice can make a brief submission to the TGA outlining the specifics of their concern which will then be actioned at the next review. If the variance in the PI/CMI is considered to be potentially serious or life threatening, a procedure for the review to be brought forward is required.

References:


4. Rivkees SA. 63 years and 715 days to the "boxed warning": unmasking of the propylthiouracil problem. *Int J Pediatr Endocrinol* 2010; Epub Jul 12.
The quality of medication information in Australia: the need for more clinical expertise and accountability

Jim R Stockigt

The current review of the Therapeutic Goods Administration is an opportunity to improve the system for updating product and consumer information on drugs

Pharmaceutical product information (PI) and consumer medicines information (CMI) are mandatory for prescription products in Australia, and government regulations specify that CMI must be consistent with PI.\(^1\) Health professionals and consumers should be able to assume that these sources are up-to-date and consistent with evidence-based best practice. However, this is not necessarily so, particularly for older medications.\(^2,3\) There is a wide discrepancy between the high-quality information available for new medications (eg, through series such as NPS RADAR [National Prescribing Service Rational Assessment of Drugs and Research]) and some existing texts\(^2-4\) that originate from pharmaceutical sponsors, who pay fees to the Therapeutic Goods Administration (TGA) for review and approval of their submitted material.

Officially sanctioned information may appear different from different perspectives: all may seem to be in order when assessed from the top down, and shortcomings may become apparent only when specific end products or outcomes are evaluated. Two examples demonstrate this problem. Current CMI for glucocorticoids fails to distinguish between the dosages for replacement and for anti-inflammatory and immunosuppressive effects, a potential health hazard for several thousand Australians with adrenal insufficiency.\(^3\) The CMI in question, presented without professional accountability, remains uncorrected 18 months after attention was drawn to it,\(^4\) and is clearly inconsistent with the corresponding PI and advice in the Australian medicines handbook.\(^5\)

In a second example, review of the PI from four different sponsors for thyroid medications identified erroneous therapeutic recommendations and the omission of well established indications or important side effects, as well as inappropriate advice on dose adjustment.\(^2\) Two years after publication of a detailed critique of the PI for these medications,\(^2\) 11 of 16 salient errors remain uncorrected.\(^6\)

When medical professionals point out necessary improvements to current PI or CMI, official responses tend to be self-affirming, legalistic and defensive, rather than receptive to evidence and the consensus of clinical expertise. For example, when it was pointed out that the instruction in CMI, “Do not take Cortate if you have an uncontrolled infection”,\(^5\) was dangerous for those with adrenal insufficiency, the TGA responded with the unexpected sophistry that this advice meant only “before you commence taking Cortate”, rather than “before you take your continuing medication”.\(^7\) A response in the general press from NPS leadership denied any need to differentiate glucocorticoid replacement from other indications.\(^8\)

What are the systemic weaknesses of Australia’s system of preparing, reviewing and updating PI and CMI?
• Australian pharmaceutical sponsors may lack the clinical resources and perspective to offer PI that reflects evidence-based best practice.
• The major publisher of PI and CMI, MIMS Australia, is restricted to publishing the TGA-approved texts. 9
• PI and CMI are currently presented without professional accountability, a prerequisite for effective review.

How can these difficulties be addressed? Some recommend a defined “use by” date for PI. 10 However, regular review would not necessarily address clinical concerns, and the cost might be prohibitive.

What else can be done?
• Regulatory authorities must abandon the now familiar response to any critique, “PI is the responsibility of the drug sponsor”, which can be used by these authorities to deny responsibility for deficiencies in that information.
• Sponsors need stronger clinical support, whether through the TGA or other means, in presenting therapeutic advice.
• Those who publish and disseminate PI and CMI, such as MIMS Australia, should be able to review, and should be accountable for, those texts. MIMS names a distinguished senior honorary editorial panel, 6 who could have a valuable role in endorsing published PI or suggesting necessary revisions.

Abundant clinical expertise is available in Australia, often concentrated and coordinated in the clinical and scientific specialty societies, that could be brought together under the auspices of the Royal Australasian College of Physicians. Consensus advice from a specialty society, rather than individuals, would diminish the potential influence of commercial interests or pressure groups.

The key to effective updating and improvement of Australian pharmaceutical information is more fluent incorporation of clinical input, as occurs for adverse drug events. A notification process, initiated by vigilant professionals and consumers, should make it possible to eliminate incorrect, misleading, ambiguous or obsolete PI and CMI. The alternative is a progressively widening gap between industry and the consumers and professionals who use or prescribe medications. Both groups have the right to expect reliable, officially sanctioned pharmaceutical information. A revision of structures within the TGA is currently in progress. 11 It would be a further setback if this opportunity to incorporate expert professional advice in the preparation and improvement of PI and CMI were overlooked.

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References
Barriers in the quest for quality drug information: salutary lessons from TGA-approved sources for thyroid-related medications

Jim R Stockigt

n iodine-replete countries, about 5% of the population have a thyroid disorder,1 of whom about a quarter will require long-term medication either to correct deficiency or to control thyroid hormone excess. In 2005, about 700 000 Pharmaceutical Benefits Scheme prescriptions were filled in Australia for thyroxine, with about 80 000 scripts for the antithyroid drugs carbimazole and propylthiouracil.2

Although no major new therapeutic agent has been introduced in the thyroid field for some years, the body of knowledge and evidence has advanced. It is important that these developments are reflected in the product information (PI) widely used by medical practitioners and a range of health professionals, who may not refer directly to current scientific literature on thyroid disorders. MIMS (Monthly index of medical specialties) annual,3 in its 30th edition in 2006, and the Australian prescription products guide (APPG) 2006, 35th edition,3 are the most commonly used compilations of PI (provided by the drug manufacturer and approved by the Therapeutic Goods Administration [TGA]). Both are mandatory pharmacy references specified by some state pharmacy boards.5,6

My review assesses whether PI-based information on thyroid-related medications as reproduced in MIMS annual 2006, MIMS Online and APPG 2006 is in accord with current peer-reviewed medical literature and contemporary therapeutic practice.

Importance of thyroid-related drug information

There are several reasons why patients taking thyroid-related medications, who number over 200 000 in Australia, need reliable information. First, they should aim for some self-sufficiency in relation to their medications, because long-term treatment and follow-up often extends beyond contact with any one medical practitioner. Second, they may need to make informed choices between therapeutic alternatives. For example, a young woman with thyrotoxicosis who has future plans for pregnancy may be offered ablative treatment, with the prospect of subsequent lifelong thyroxine replacement therapy that will need to be adjusted during pregnancy. Her alternative of antithyroid drug treatment, with the possibility of remission or recurrence, might be dismissed if she were given poorly documented advice about the safety of antithyroid drugs during pregnancy and lactation. Third, there is potential for ill-advised dose adjustment, failure to recognise side effects and, at times, misuse1 of thyroid-related drugs.

Sources of drug information

The stated aim of the 2006 MIMS annual is to serve as “the byword for accurate, reliable, comprehensive and independent medicines information”. It also states that “Prescribers, and health care professionals in general, need to be confident in today’s litigation-conscious environment that the information used as decision support, in both electronic and print formats, is reliable, accurate, from a trusted source AND reflects the current APPROVED information”.1 Further, the title page of the 2006 MIMS annual states that “Product monographs in MIMS annual represent Therapeutic Goods Administration (TGA) approved product information, which is the result of years of research and development by the sponsor company and of painstaking evaluation and review by the Drug Safety and Evaluation Branch of the TGA”. 3 These statements imply an intention to offer both pharmaceutical information and reliable clinical advice. It follows that patient care can be influenced by the quality and accuracy of the information in PI supplied by pharmaceutical manufacturers or sponsors, and then endorsed by the TGA. This potential link to clinical decisions mandates accountability for PI-based drug information.

ABSTRACT

• Product information (PI) for thyroid-related medications endorsed by the Therapeutic Goods Administration, as reproduced in the commonly used compilation publications June 2006 MIMS (Monthly index of medical specialties) annual, MIMS Online and the Australian prescription products guide 2006, was evaluated to see whether it reflects contemporary therapeutic practice.

• Compared with current medical literature, these PI-based sources provide inadequate, inaccurate or outdated therapeutic directives. Examples include:
  ➢ Incorrect advice that thyroxine therapy should always begin at very low dosage.
  ➢ Failure to recommend increased thyroxine dosage early in pregnancy (thus placing the offspring of women being treated for hypothyroidism at risk of impaired fetal brain development).
  ➢ Incorrect and potentially unsafe advice to treat thyrotoxicosis with stable iodide in late pregnancy.
  ➢ Failure to advise serial adjustment of antithyroid drug dosage until after a patient becomes euthyroid (this can result in iatrogenic thyroid dysfunction).
  ➢ Outdated advice that antithyroid drugs are not compatible with breastfeeding.

• Recent initiatives to upgrade consumer medicine information (CMI) appear to accept PI-based sources as a reliable benchmark for CMI. That inference is not warranted for thyroid-related medications.

• Accountability for the updating of clinical information in PI needs to be defined, and the process for updating PI may need to be modified.

• Quality drug information, both PI and CMI, depends on fluent, evidence-based collaboration between suppliers, regulators, prescribers, specialist clinicians and consumers.

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Contentious, unsafe, omitted or undocumented recommendations for thyroid-related medications, as reproduced in MIMS and APPG from approved product information (my emphasis indicated by italics)

THYROXINE

Initiation of therapy

“In all cases, Orrox [Sigma] should be initiated at not more than 50 microgram/day and gradually increased . . .”

Critique: This absolute restriction, based on caution in initiating thyroxine therapy in elderly patients with hypothyroidism, may be quite inappropriate. After near-total thyroidectomy in an euthyroid healthy adult, full replacement dosage should be used.8–10,13 to avoid unnecessary iatrogenic hypothyroidism. For newly diagnosed hypothyroidism in pregnancy, 1.5–2.0μg/kg per day is now recommended as the initial dosage.14

Quality of evidence: Reference 8-10 (II-2, B); 13 (IV, B); 14 (III-3, B).

Dose modification in pregnancy

“For women with established hypothyroidism, thyroxine replacement generally needs to be increased by 25 to 40% during pregnancy, based on measurements of TSH and thyroxine levels at the end of the first and second trimesters.”

Critique: Dosage does need to be increased, particularly to avoid any degree of hypothyroidism in the first trimester, when fetal brain development is critically dependent on maternal thyroxine.15 Adjustments based on measurements at the end of the first trimester are likely to be too late to address this need.14 Contemporary advice is to optimise the dose of thyroxine when pregnancy is anticipated, and to increase dosage by about 30% when pregnancy is confirmed.14 In addition, the statement “clinical experience does not indicate any adverse effects on the foetus when the thyroid agents are administered during pregnancy” would be more pertinent if it emphasised the need to increase dosage early in pregnancy to avoid the adverse effect on the fetus of under-replacement.14,15

Quality of evidence: Reference 14 (III-3, B); 15 (II-2, B).

Indications incompletely documented

Further indications for the use of thyroxine that have been omitted are:

1. Thyroxine may be used in conjunction with an antithyroid drug (block–replace regimen) for the management of thyrotoxicosis.8,16

2. Thyroxine may be used in euthyroid goitre, especially before nodularity has developed, aimed at inhibiting goitre growth by suppressing TSH.17

Quality of evidence: Reference 8, 16, 17 (III-3, B).

CARBIMAZOLE

Thyrotoxicosis in pregnancy

“Neo-Mercazole [Link] should be discontinued three to four weeks before delivery and a course of iodine should be substituted.”

Critique: This recommendation is not based on any evidence and is contrary to current practice. Substitution of stable iodide for an antithyroid drug late in pregnancy can be a serious error and is contraindicated. Excess iodide can cause fetal goitre and neonatal hypothyroidism, especially in premature infants.18,19 High-dose iodide should not be given in pregnancy, except when necessary, as preparation for surgery.19 If required, carbimazole can be safely continued, at the lowest possible dose.

Quality of evidence: Reference 18, 19 (IV, B).

Breastfeeding

“Infants should not be breastfed by mothers taking carbimazole.”

Critique: Breastfeeding was proscribed in women taking either carbimazole (methimazole) or propylthiouracil until about 20 years ago.20 On current data, treatment is safe in standard dosage, although carbimazole is detectable in breast milk.16,21 Inadvertent over-treatment of lactating women produced no adverse effect on infants.22 Propylthiouracil is often preferred to carbimazole as transfer to milk is less.21

Quality of evidence: Reference 16, 21, 22 (III-3, B).

Review of dosage

“Once a remission has been secured, maintenance dosage should be continued for at least 12 months, and up to two years of treatment may be required.”

Critique: This recommendation is unclear and confusing, not based on any evidence and contrary to current practice. The response cannot be classified as remission while an antithyroid drug is still required. When control has been achieved, failure to decrease or cease dosage can result in serious iatrogenic hypothyroidism (see dose adjustment strategy for propylthiouracil).

Coordination with radioiodine

“Neo-Mercazole [Link] should be stopped temporarily at the time of administration of radioiodine.”

Critique: This recommendation will limit the efficacy of radioiodine. Carbimazole needs to be stopped several days before and for several days after radioiodine administration,8,9 to avoid blocking its incorporation into thyroglobulin (the same applies to propylthiouracil).

Quality of evidence: Reference 8, 9 (III-3, B).

PROPYLTHIOURACIL

Dose review and modification

“After control of thyrotoxicosis, the dose of propylthiouracil should be gradually decreased to 50mg twice daily.”

Critique: Dosage of both carbimazole and propylthiouracil needs to be reviewed and adjusted before achieving normal hormone levels. Delayed dose adjustment, as advised, can result in severe over-treatment. Dose reduction is appropriate when thyroid hormone levels decrease by 30%–50%.8,9

Quality of evidence: Reference 8, 9 (IV, C).

Breastfeeding

“Breastfeeding should be terminated prior to initiation of therapy.”

Critique: This recommendation was superseded by new data 20 years ago (see comment for carbimazole).16,20,21 Propylthiouracil is often preferred to carbimazole because transfer to milk is less.21

Quality of evidence: Reference 16, 20, 21 (III-3, B).

Inaccurate explanation of mode of action

“Propylthiouracil blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) by inhibiting incorporation of iodide into tyrosine.”

Critique: This conversion involves removal rather than incorporation of iodine.

Adverse effects incompletely documented

Further adverse effects of propylthiouracil are not listed:

1. Serious hepatotoxicity.16,20

2. Immune vasculitis syndrome, with positive antineutrophil cytoplasmic antibody.16

Quality of evidence: Reference 16, 20 (IV).

Maximum dosage

“Patients with severe hyperthyroidism may require up to 2 g/day.”

Critique: Dosage of 2 g daily has no record of safety. Dosage of 1200 mg daily is the upper limit recommended for severe hyperthyroidism or thyroid storm.16

Quality of evidence: Reference 16 (III-3, B).

LIOXYTHYRONINE

Unresponsiveness to thyroxine

“In myxoedema unresponsive to thyroid [extract] or thyroxine, liothyronine is essential.”

Critique: There are no authenticated reports of acquired resistance to thyroxine, with retained responsiveness to liothyronine. Other causes of apparent unresponsiveness to thyroxine, such as poor compliance, impaired absorption and insufficient dosage of thyroxine, must be checked before considering liothyronine.

Other hypometabolic states

“In other conditions of the hypometabolic state, the usual daily dosage is 20 to 60 microgram divided and administered two or three times daily.”

Critique: This appears to support use of liothyronine in hypometabolic states other than hypothyroidism. Such conditions have not been confirmed to exist, and this recommendation endorses a common mode of thyroid hormone misuse.1

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MIMS = Monthly index of medical specialties annual.9 APPG = Australian prescription products guide.4 TSH = thyroid stimulating factor. “Quality of evidence” according to National Health and Medical Research Council (NHMRC) — level of evidence, I–IV; grade of recommendation, A–D.12
Contentious points in PI-based sources for thyroid-related medications

There are numerous discrepancies when information on thyroid-related medications in the PI-based June 2006 MIMS annual, MIMS Online and APPG 2006 is compared with the current medical literature and with Australasian and international reviews. Major points of contention that have a direct impact on patient care are summarised in the Box.

Where possible, evidence for the critiques of the PI has been presented according to the notation of National Health and Medical Research Council (NHMRC) guidelines (level of evidence [I–IV] and grade of recommendation [A–D]). In some, the NHMRC level of supporting evidence does not appear high, as randomised trials have not been performed — many thyroid-related medications have been in use for decades and their introduction pre-dates stringent documentation. However, the currently available lower-level evidence has been confirmed in endocrinology clinical practice over many years and has been incorporated as current best practice.

Some examples of contentious points, which are discussed further in the Box, include:

- A healthy euthyroid adult need not experience a period of iatrogenic hypothyroidism after near-total thyroidectomy, as would occur if PI-based guidelines for commencement of thyroxine treatment (“In all cases, Oroxine [Sigma] should be initiated at not more than 50 microgram/day . . .”) [eg, MIMS annual 2006. Oroxine. Precautions: Initiation of therapy)] were followed.
- Further, it is apparent from clinical practice that continuation of antithyroid drug without dose modification until a patient is shown to be euthyroid can lead to serious over-treatment. (“After control of thyrotoxicosis, the dose of propylthiouracil should be gradually decreased to 50 mg twice daily.” [eg, MIMS annual 2006. Propylthiouracil. Use in pregnancy]). If a patient were then to abruptly stop the antithyroid drug either by own choice or on medical advice, the thyrotoxicosis would probably recur.
- The recommendation that liothyronine can be used for “myxoedema unresponsive to . . . thyroxine” and for “other conditions of the hypometabolic state” [eg, MIMS annual 2006. Tertroxin [Sigma]. Dosage and administration], is contentious and potentially harmful. There is no evidence-based confirmation of this ill-defined group of conditions actually exists; this recommendation provides an apparent endorsement of a common mode of thyroid hormone misuse.

Thus, if such recommendations for the use of thyroid-related medications, as espoused in the PI and thus in MIMS and APPG, were mistakenly interpreted as firm guidelines for prescribing practice, these texts would legitimise potential misuse of medication, while implying that several established therapeutic strategies are “off label”.

Recommendations on the use of iodide

The formulation, source, dosage and adverse effects of iodide are not documented in MIMS or APPG; no PI has apparently been submitted, as there is no commercial sponsor. Nevertheless, these texts make imprecise or dubious recommendations for its use within the information pertaining to other thyroid medications.

The recommendation that high-dose iodide should be used routinely in preparation for surgery in thyrotoxicosis (eg, MIMS annual 2006. Neo-Mercazole [Link]. Dosage and administration — last paragraph) is erroneous. While short-term high-dose iodide does temporarily inhibit thyroid hormone release and reduces the vascularity of the gland in Graves disease, it has no beneficial effect on thyroid blood flow in toxic multinodular goitre (quality of evidence: III-2, B). It should be noted that sustained iodide excess can exacerbate thyrotoxicosis and can impair the response to antithyroid drugs, with the potential for severe drug-resistant thyrotoxicosis that may require emergency surgery (quality of evidence: IV, B).

Formulation of consumer medicine information

The TGA has initiated a consultancy to improve the range and quality of consumer medicine information (CMI), which it also endorses. The preliminary discussion paper defines PI as the benchmark for CMI. While that document acknowledges that problems arise if PI is not kept up to date, there is no clear perception of any need to go beyond PI sources in preparing CMI. That current PI-based sources can differ widely from contemporary therapeutic practice is a reality that should be considered in preparing CMI. Under present arrangements, CMI can be no better than the PI supplied by manufacturers or sponsors of repackaged imported products.

Mechanisms to improve and update PI and CMI

According to current regulations, initiatives to update or alter the PI of prescription medications require a manufacturer or sponsor to apply to the TGA and pay a fee for review of a revised submission. The TGA does not normally initiate changes in PI. While there is some provision for a sponsor to make “self-assessable” changes in PI as defined, it is unlikely that the problematic recommendations identified here could be altered by “self-assessable” revision under current regulations. Thus, each of the four companies that market the medications listed in the Box would need to make a separate submission to the TGA to initiate revision; there is no commercial incentive to do so. The situation regarding iodide is unusual because it has no commercial sponsor; accountability for the suggestions on its use is undefined.

The quality of information on thyroid-related medications in the PI of each drug, and thus in MIMS and APPG, is deficient to an extent that requires prompt review. The established mechanisms for updating PI are unlikely to achieve this, especially as the accountability for some information in these texts is undefined. An initiative to revise out-of-date or inaccurate sections could involve Australian clinicians who observe the effects of thyroid-related...
medications and are acquainted with relevant medical literature. Their advice can be sought, either directly through the Endocrine Society of Australia, or through the Therapeutics Committee of the Royal Australasian College of Physicians. A clearly defined, professional peer review process, the cornerstone of reputable medical literature, might improve the information currently available for both new and long established thyroid-related medications.

Addendum: Review of sequential MIMS annuals indicates that there has been no substantive change to the entries for carbimazole (Neo-Mercazole) or propylthiouracil since 1985. The entry for lithium (Tertroxin) was updated in 1988 and that for thyroxine (Oroxine) in 1990. Advice that dosage of thyroxine should be increased in pregnancy was added in 2004. Storage instructions for thyroxine were revised in 2006.

Competing interests
I received travel assistance from Abbott, manufacturer of thyroid products in the United States, to attend and present at the American Thyroid Association meeting in Vancouver (2004).

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References
20 Azizi F. Thyroid function in breast-fed infants is not affected by methimazole-induced maternal hypothyroidism. J Endocrinol Invest 2003, 26: 301-304.

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NAME OF THE MEDICINE

Propylthiouracil

Chemical Name: 1,2-dihydro-6-propyl-2-thioxopyrimidine-4-one

The molecular weight of the compound is 170.2, the molecular formula is C$_7$H$_{10}$N$_2$OS and the CAS registry number is 51-52-5.

DESCRIPTION

Propylthiouracil is a thioamide derivative which occurs as a white crystalline powder, odourless with a bitter taste, very slightly soluble in water, sparingly soluble in ethanol and soluble in solutions of alkali hydroxides or ammonia.

PTU™ 50 mg Tablets are white, round, biconvex and uncoated. One side is debossed ‘PRESTAB’ and other side is plain.

PHARMACOLOGY

Category: Antithyroid

Propylthiouracil blocks the peripheral conversion of thyroxine (T$_4$) to triiodothyronine (T$_3$) by inhibiting incorporation of iodide into tyrosine.

Propylthiouracil is rapidly absorbed. The half-life in plasma approximates 2 hours (in anuric patients T½ 8.5 hours). Protein binding of propylthiouracil is approximately 75%. The drug is metabolized in the liver and is excreted in the bile (primary route) with approximately 30% being excreted in the urine as metabolites or whole drug. Propylthiouracil does not interfere with the action and the release of exogenous thyroid hormone. Clinical response, therefore, does not occur until circulating and colloid-stored thyroid hormone is utilised, and as such depends in part on the amount of colloid in the gland. The rapid fall in serum triiodothyronine T$_3$ concentration, before serum thyroxine (T$_4$) levels fall, parallels a clinical improvement in the thyrotoxic patient, and is generally seen after the first week. The patient may become euthyroid after 4-6 weeks.

Propylthiouracil does not interfere with the effectiveness of thyroid hormones given by mouth or injection. Prolonged administration of propylthiouracil may result in hyperplasia of the thyroid gland due to pituitary thyrotrophic hyperactivity induced by diminished thyroxine secretion.

INDICATIONS

Propylthiouracil is an antithyroid drug indicated for the total treatment of hyperthyroidism or in the treatment of the thyrotoxic patient prior to surgery or radioactive-iodine therapy.

CONTRAINDICATIONS

Patients who are known to be hypersensitive to propylthiouracil or related thioamide derivatives.
PRECAUTIONS

In preparing patients for surgery, the administration of iodine is recommended concomitantly with propylthiouracil to decrease the vascularity and friability of the thyroid gland.

Although propylthiouracil is used for the total treatment of hyperthyroidism, duration of treatment necessary to produce a prolonged remission varies from 6 months to several years, with an average duration of one year. Remission has occurred in at least 50% of patient's 6-12 months after cessation of medication.

In view of the fact that hypothyroid patients seem to have poor adrenergic nervous function, use with caution in patients with asthma.

Patients should be closely supervised during prolonged propylthiouracil therapy because of the likelihood of agranulocytosis. Patients should be warned to report immediately any evidence of illness, particularly sore throat, skin eruptions, fever, chills, headache, and malaise. All patients receiving propylthiouracil should have regular full blood counts as well as dose monitoring of liver and thyroid function tests (See "Interaction with Other Medicines" and "Adverse Effects").

Regular thyroid function tests are recommended in patient monitoring (recommended prior to initiation of therapy, at monthly intervals during stabilization, then every 2 to 3 months) viz Free (unbound) Serum Thyroxine (T4) levels, Total Serum T4 levels, Serum Thyrotropin (TSH), Total Serum Triiodothyronine (T3). Liver Function Tests are also recommended at periodic intervals during therapy.

Use in Pregnancy
Propylthiouracil is pregnancy category C

Propylthiouracil freely crosses the placenta, and the safety of this product for use during pregnancy has not been fully established. Propylthiouracil may damage the foetal thyroid and produce foetal hypothyroidism and neonatal goitre, or cause congenital abnormalities in the neonate (vide infra).

In administering propylthiouracil during pregnancy, careful consideration should be given to the dosage for individual patients to provide the required therapeutic effect compatible with minimum risk to the foetus from potential toxicity. The dose should be set as low as possible since there is evidence that neonatal goitre is less likely if the mother receives less than 100 mg of propylthiouracil per day. After control of thyrotoxicosis, the dose of propylthiouracil should be gradually decreased to 50 mg twice daily. If there is the slightest suspicion of hypothyroidism in the pregnant patient, the drug should be temporarily discontinued and thyroid hormone given.

Three cases of scalp defects in the offspring of mothers, and two siblings with aplasia cutis in one mother, who were on methimazole, a related thioamide derivative, have been reported.

Use in Lactation
Propylthiouracil is excreted in breast milk. Breast feeding should be terminated prior to initiation of therapy.

Interactions with Other Medicines
Because propylthiouracil can cause hypoprothrombinemia, extreme caution is advised in patients receiving oral anticoagulants or heparin. Prothrombin times should be carefully monitored during therapy.

Agranulocytosis Producing Medications
Concurrent use may increase the risk of agranulocytosis.

Effect on Laboratory Tests
Prothrombin Time, Serum alkaline phosphatase, Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic-pyruvic transaminase (SGPT) levels may be increased.

ADVERSE EFFECTS

Note: Incidence of adverse effects is directly related to dosage.

The overall incidence of side effects with propylthiouracil is of the order of 3%.

Incidence less frequent: Inhibition of haemopoiesis (agranulocytosis, granulocytopenia, leucopenia, thrombocytopenia) is the most serous side effect. The incidence of agranulocytosis approaches 0.5%. Agranulocytosis usually occurs during the first two months of therapy and then the incidence gradually declines. Mild leucopenias occur more frequently, and approximately 10% of untreated hyperthyroid patients have leucocyte levels below 4.0 x 10^9/L. It should be noted that about 10% of patients with untreated hyperthyroidism have leucopenia (white blood cell count 4000/cu mm), often with relative granulocytopenia.
Incidence rare:
- Yellowing of eyes and skin (cholestatic jaundice)
- Loss of hearing (ototoxicity)
- Swollen lymph nodes (lymphadenopathy)
- Unusual bleeding or bruising (hypoprothrombinemia, factor VII or proconvertin deficiency, thrombocytopaenia)
- Unusual increase or decrease in urination, backache, swelling of feet or lower legs (nephritis)

Signs of overdosage or hypothyroidism: Changes in menstrual periods, coldness, constipation, dry, puffy skin, headache, listlessness, muscle aches, sleepiness, tiredness, unusual weight gain, weakness.

Signs of thyrotoxicosis or inadequate therapy: Diarrhoea, fever, irritability, listlessness, rapid or irregular heartbeat, vomiting, weakness.

Those indicating need for medical attention only if they continue or are bothersome.

Incidence more frequent: Itching

Incidence less frequent: Dizziness, joint pain, loss of taste, nausea and vomiting (possible overdose), numbness or tingling of fingers, toes, or face (peripheral neuropathy, possible overdose), skin rash (hypersensitivity). Note: may disappear spontaneously with continued treatment; appears to be dose-related. Stomach pain.

Incidence rare: Darkening of skin, lightening of hair colour, loss of hair, sore, red, watery eyes (recurrent keratitis, conjunctival disorders).

Hepatotoxicity: Propylthiouracil-related hepatotoxicity is a major but rare side effect. The frequency ranges from 0.1 percent to 0.2 percent and takes the form of an allergic hepatitis accompanied by laboratory evidence of hepatocellular injury. This includes markedly elevated amino-transferase levels and submassive or massive hepatic necrosis on biopsy. The danger of permanent hepatic damage should be kept in mind. The best way of preventing propylthiouracil hepatotoxicity is careful screening of patients considered for treatment.

Vasculitis: Vasculitis is a rare complication of propylthiouracil therapy. Serological evidence consistent with lupus erythematosus develops in some patients, fulfilling the criteria for drug-induced lupus. There are 32 cases of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis in association with anti-thyroid medication reported in the English literature. Approximately 90% of cases related to propylthiouracil. The clinical features of anti-thyroid drug induced ANCA-positive asculitis include renal involvement (67%), arthralgia (48%), fever (37%), skin involvement (30%), respiratory tract involvement (27%) and other manifestations (18%).

DOSAGE AND ADMINISTRATION

Propylthiouracil is administered orally, usually in 2 to 4 equal doses at 12 to 6 hourly intervals respectively.

Dosage in Adults
The usual initial controlling dose of propylthiouracil is 200-400 mg daily (range 100-1200 mg) in divided doses (three doses at eight-hour intervals or four doses at six-hour intervals) until the patient becomes euthyroid.

NB: Patients with severe hyperthyroidism may require up to 1,200 mg a day.

Maintenance Dose: 50-800 mg daily in two to four divided doses.

Thyrotoxic Crisis: Concomitant with the administration of other agents, e.g. iodine, adrenergic blocking agents, and general supportive measures, the recommended dose of propylthiouracil is 800-1200 daily in divided doses administered orally or by naso-gastric tube.

Dosage in Children

Initial: Calculated on 50 mg/m² of body surface three times a day.

6-10 years: 50 to 300 mg a day in two or three divided doses.

10 years and over: 150 to 600 mg a day divided into three doses at eight-hour intervals.

Maintenance Dose: 50-100 mg daily as determined by response.
Neonatal thyrotoxicosis: 10 mg per kg of body weight a day in divided doses.

OVERDOSAGE

Agranulocytosis is the most serious adverse effect resulting from overdose and/or prolonged administration. Hypothyroidism may result from prolonged therapy (See "Adverse Effects").

General management of overdosage may consist of gastric lavage, observation, and symptomatic and supportive therapy.

Treatment is directed at the specific adverse effect e.g. in bone marrow depression, treatment by way of blood transfusion of fresh whole blood, antibiotics, and corticosteroids are used. Prothrombin deficiency associated with a haemorrhagic diathesis may be counteracted by phytonadione.

In Australia, contact the Poisons Information Centre on 13 11 26 for further advice on overdose management.

PRESENTATION

PTU™50mg Tablets contain 50 mg of the active ingredient propylthiouracil. The inactive ingredients are lactose, magnesium stearate, povidone, sodium lauryl sulphate and maize starch. PTU™ 50mg Tablets are supplied in bottles containing 100 tablets. Store below 30°C.

Phebra Product Code: TAB001

AUST R 13319

POISONS SCHEDULE

ScheduleS4 – Prescription Only Medicine.

SPONSOR

Phebra Pty Ltd, 332 Burns Bay Road, Lane Cove NSW 2066, Australia.
Telephone: 1800 720 020

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