




EMLc
ATC codes: **H03BB02**

Indication	Thyrotoxicosis ICD11 code: 5A02.Z
INN	Thiamazole
Medicine type	Chemical agent
List type	Core (EML) Complementary (EMLc)
Formulations	Oral > Solid: 5 mg ; 10 mg ; 20 mg
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	carbimazole (ATC codes: H03BB01)
Patent information	Patents have expired in most jurisdictions Read more about patents . 
Wikipedia	Methimazole 
DrugBank	Methimazole 

Expert Committee recommendation

The Committee recommended the addition of methimazole with a square box to the core list of the EML and to the complementary list of the EMLc for use as first-line therapy for hyperthyroidism. The square box listing should specify carbimazole as a therapeutically equivalent alternative. The Committee recommended that propylthiouracil should remain on the core list of the EML for use in patients during the first trimester of pregnancy, and for other patients in whom alternative first-line treatment is not appropriate or available. The square box should be removed from the listing. The Committee also recommended that propylthiouracil should remain on the complementary list of the EMLc for use in patients for whom alternative first-line treatment is not appropriate or available. The Committee considered that the available evidence indicated that efficacy of methimazole is at least equivalent to propylthiouracil. Compared to propylthiouracil however, methimazole demonstrated a more favourable safety profile with fewer reported major adverse events. The Committee noted that propylthiouracil remains the treatment of choice in some patients and therefore should remain available.

Background

The application requested: • inclusion on the core list of the EML and EMLc of methimazole (INN thiamazole) with a square box for the first line management of Graves' hyperthyroidism in children and non-pregnant adults; • transferring the current EML listing for propylthiouracil from the core to the complementary list, and removal of the square box. • Inclusion of a note with the listing of propylthiouracil specifying use only when alternative first-line treatments are not appropriate or available, to reinforce its place as a second-line therapy. Propylthiouracil (PTU) with a square box has been included on the core list of the EML since the first list in 1977. In 2007, it was added (without a square box) to the complementary list of the EMLc. The EMLc Subcommittee noted that PTU was licensed for use in children aged over 6 years, although in some settings carbimazole (CMZ) was the more commonly used drug. The EMLc Subcommittee decided to list PTU but recommended the role of CMZ in children be reviewed (1).

Public health relevance

Graves' disease is the most common cause of hyperthyroidism. Women are affected more frequently than men at a ratio of 8:1, most commonly in the third to fifth decade of life (2). A meta-analysis of European studies estimated a mean prevalence rate of 0.75% for males and females combined and an incidence rate of 51 cases per 100 000 per year with a significant influence of ethnicity and iodine nutrition (3). Among children, Graves' disease represents more than 90% of the cases of hyperthyroidism with an incidence ranging from 0.1 per 100 000 children and 3.0 per 100 000 adolescents per year (4).

Benefits

The application identified four randomized controlled trials (RCTs) that compared the effectiveness of PTU and MMI in adults and one retrospective study in children and adolescents. The trials in adults found MMI to have similar or greater effectiveness than PTU at reducing or normalizing thyroid hormone concentrations (5–8). The paediatric study found no significant difference in the mean duration for normalization of serum T4 concentration between MMI (1.7 ± 1.0 months) and PTU (2.3 ± 2.4) treated patients (9). Two RCTs evaluated the effect of MMI (10) and CMZ (11) taken once, twice or three times daily. The results indicated that once daily dosing is as effective as multiple daily dosing. The application acknowledged that in general, less information was available for CMZ but because CMZ is metabolized to MMI after absorption, it was assumed that data that apply to MMI also apply to CMZ.

Harms

Overall, both PTU and MMI/CMZ all present with minor and major adverse events in adults and in children. However, major adverse events were less commonly reported for patients receiving MMI/CMZ. Common minor side-effects for these medicines include pruritis, skin rash, urticaria and arthralgias. Major adverse events are uncommon but include agranulocytosis, hepatic failure, vasculitis and fetal malformations. In the RCT by Nakamura et al (5), the overall incidence of adverse events was higher in the PTU group than the MMI 30 mg/d group (51.9% vs 30%). The percentage of patients who showed aspartate aminotransferase (AST) and alanine aminotransferase (ALT) higher than double the upper range of the normal standard was significantly higher for the PTU group compared to the MMI 30 mg/d group (26.9% vs 6.6%). Skin eruption or urticaria was similar between groups. Leukocytopenia (less than 1000/mm³) was observed in five patients in the PTU group only. A retrospective cohort study of 71 379 Taiwanese patients found MMI/CMZ to be associated in a dose-dependent manner with an increased risk for hepatitis compared to PTU. However, no significant difference in risk was observed between groups for acute liver failure or cholestasis (12). In the paediatric retrospective study, minor adverse events were observed more frequently among PTU treated patients compared to MMI treated patient (31.9% vs 25.0%), although the difference was not significant. The incidence of liver dysfunction was significantly higher among PTU treated patients (18.9% vs 6.3%) (9). A 2000 RCT involving 40 children found no difference in side-effects between patients receiving PTU or MMI within the same age groups (13). Agranulocytosis has been observed with both MMI/CMZ and PTU (14). There have been reports of PTU-related liver failure and death in adults and children (15), where the risk is five times higher in children than in adults. Between 1990 and 2008, a total of 23 PTU-related liver transplants were reported, and 30% of recipients were paediatric patients. No MMI-related liver transplants were reported in the same time period (16). Antineutrophil cytoplasmic antibodies (ANCA) vasculitis has been reported, more often related to PTU than MMI (17, 18). A high prevalence of birth defects in children exposed to anti-thyroid drugs in early pregnancy has been reported (19). It is not clear whether MMI and CMZ lead to a higher prevalence of fetal malformations compared to PTU. Some studies have shown similar rates of fetal defects with both drugs (12). However, this rate may not be higher than the rate of malformations in the control population (20). In contrast, a recent metanalysis showed an increased risk of neonatal congenital malformations associated with MMI, but not PTU when compared to no antithyroid medicines exposure (21). However, the fetal malformations associated with PTU may be less severe and easier to correct than those associated with MMI and CMZ.

Cost / cost effectiveness

Costs of PTU, MMI and CMZ vary considerably between countries. The application compared the calculated costs for one month of treatment with PTU, MMI or CMZ. For the induction treatment period, costs ranged from US\$ 7 to US\$ 37 per month for MMI, US\$ 18 to US\$ 27 per month for CMZ and from US\$ 3.5 to US\$ 68 per month for PTU. For the core treatment period, costs ranged from US\$ 3.50 to US\$ 18.50 per month for MMI, and from US\$ 9 to 13.50 per month for CMZ and US\$ 1.80 US\$ 34 per month for PTU.

WHO guidelines

There are no WHO guidelines currently available for the management of Graves' disease. The 2018 European Thyroid Association guidelines for management of Graves' disease recommend MMI as preferred treatment for newly diagnosed patients (both adults and children). The guidelines further recommend that MMI-treated women should be switched to PTU when planning pregnancy and during the first trimester (22). The 2016 American Thyroid Association Guidelines also recommend use of MMI in almost all patients. PTU is recommended for patients during the first trimester of pregnancy, in the treatment of thyroid storm, and in patients with minor reactions to MMI who refuse radioactive iodine therapy or surgery (23).

Availability

Usually, only one of CMZ or MMI is available in a given country reflecting differences in regulatory approval in different jurisdictions. PTU is available globally.

Other considerations

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support the requests made in the application and considered the evidence presented in the application to be deficient.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, October 2007 (including the Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 950). Geneva: World Health Organization; 2008. Available from https://apps.who.int/iris/bitstream/handle/10665/43745/WHO_TRS_946_eng.pdf, accessed 30 October 2019.
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