carbiMAZOLe

Newborn use only

2023

Alert	In Australia, only carbimazole is available and methimazole is not available. Obtain baseline blood count and liver function tests prior to starting therapy.
Indication	Thyrotoxicosis.
Action	Inhibits thyroid peroxidase and consequently synthesis of thyroid hormone.
Drug type	Antithyroid agent. Tionamide derivative. Carbimazole is a prodrug of methimazole, which is the active metabolite.
Trade name	Neo-Mercazole
Presentation	5 mg tablets 2mg/mL oral suspension, prepared in-house by pharmacy
Dose	• Obtain baseline blood count and liver function tests prior to starting therapy. • **Starting dose: 750 micrograms/kg/day in 1-3 divided doses.[1-3]** • *In practice, the dose is given as the nearest 1/4th tablet (1.25 mg). Consult hospital pharmacy if a suspension can be made for inpatients.[4] • Titrate the dose as per free T4 (FT4) levels – reduce the dose by 25% every 36 or 48 hours* if FT4 normal. TSH normalisation may lag.[2] • Continue treatment until infant thyroid receptor antibodies have resolved. • ***NOTE:** Titrating depends on practicalities of tablet size and the availability of compounding. The 5mg tablets can only be reliably cut into ¼, thus any dose changes need to be in multiples of this, or varying the frequency. e.g. an increase would need to be ¼ daily to ¼ BD.
Dose adjustment	Therapeutic hypothermia – not applicable. ECMO – No information. Renal impairment – No information. Hepatic impairment – Refer to contraindications section. To discuss with paediatric endocrinologist.
Maximum dose	
Total cumulative dose	
Route	Oral
Preparation	Tablet Oral suspension (extemporaneously compounded by hospital pharmacy)
Administration	Administer orally with or without feeds
Monitoring	Prior to starting therapy, obtain complete blood cell count and liver function tests.[5] Thyroid function tests – Once or twice a week to start with, then reduce weekly to fortnightly once stable.[1, 3] Obtain two normal thyroid function tests once carbimazole ceased to ensure ongoing euthyroid status.[2, 6]
Contraindications	Previous history of adverse reactions to carbimazole or to any of the excipients in the composition.[7] Retrosternal goitre.[7] Serious pre-existing haematological conditions.[7] To discuss with paediatric endocrinologist. Severe hepatic insufficiency.[7] To discuss with paediatric endocrinologist.
Precautions	Serum digitalis level may be increased when hyperthyroid patients on a stable digitalis glycoside regimen become euthyroid, reduce dose of digitalis glycoside if required.[7] Metabolism of beta-adrenergic blockers may be increased in patients with hyperthyroidism, reduction in dosage of beta-blockers may be required when patients become euthyroid.[7, 16]
Drug interactions	Anticoagulants: carbimazole is a vitamin K antagonist and hence the effect of anticoagulants could be intensified. Consider additional monitoring of prothrombin time/international normalised ratio.[7, 15] Theophylline: hyperthyroid people may metabolise theophylline faster than euthyroid people. Monitor theophylline concentration and for adverse effects when starting treatment until patient is stable. Consider adjusting theophylline dose if required.[7, 15, 16] Prednisolone: co-administration may increase clearance of prednisolone.[7] Erythromycin: co-administration may reduce clearance of erythromycin.[7]
Adverse reactions	Leukopenia, agranulocytosis[5] Pruritic rash, jaundice, acolic stools or dark urine, arthralgias, abdominal pain, fatigue, fever, or pharyngitis[5] Stevens-Johnson syndrome[1]

	Vasculitis[1]
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Tablets: stable until expiry date written on the bottle Oral suspension: up to 19 days, check with local pharmacy.[17]
Storage	Tablets: store below 25°C. Protect from moisture.[7] Oral suspension: Refrigerate (2-8°C).[17]
Excipients	Neo-Mercazole contains lactose monohydrate, sucrose, maize starch, magnesium stearate, purified talc, acacia, iron oxide red and gelatin.[7]
Special comments	
Evidence	**Background** About 0.2% of pregnant women have been estimated to have Graves disease and about 1% of the infants born to these women are described as having hyperthyroidism.[8] Thyroid function in fetus of mothers with Graves disease is affected by the transplacental passage of thyroid blocking or stimulating antibodies (both may coexist) and by antithyroid drugs.[3] Neonatal hyperthyroidism occurs in less than 5% of neonates born to mothers with autoimmune hyperthyroidism, corresponding to an incidence of 1 in 50,000 neonates.[9] Most cases of neonatal thyrotoxicosis are transient, secondary to maternal Graves disease. In these cases, hyperthyroidism generally resolves in 4-5 months after TSH receptor–stimulating antibodies (TRAb) clearance. Neonatal hyperthyroidism can also occur secondary to activating mutations in the thyroid-stimulating hormone receptor (TSHR) or guanine nucleotide-binding protein (GNAS) gene (McCune-Albright syndrome).[10] The higher the maternal TSI or TRAb level in the third trimester of pregnancy, the higher the risk of neonatal thyrotoxicosis which is most likely when the TSI or TRAb is more than three to five times the upper normal limit but can occur at lower levels.[2] Canadian consensus guidelines suggest TRAb levels should be determined between 20 and 24 weeks of pregnancy. If maternal TRAb levels are negative, no specific GD-related follow-up is necessary. If TRAb levels are unavailable or positive, the newborn should be regarded as being "at risk" for hyperthyroidism.[1] The appearance of neonatal hyperthyroidism may be delayed by a few days if the mother was on anti-thyroid medications during pregnancy [6] or rarely due to the simultaneous transfer of maternal thyroid blocking antibodies.[6] **Efficacy** A variety of doses have been used and recommended, but no good evidence to support one dose over another. Preterm infants may have altered pharmacokinetics. Neonates may become hypothyroid either from overdose or resolving disease. The case series/reports in neonates are summarised below. A prospective observational study reported the course of thyroid function and clinical outcomes in neonates born to women with Graves disease. Carbimazole was given in a daily dosage of 1 mg/kg for a mean duration of 5 weeks when free T4 (FT4) were >35 pmol/L between days 2 and 15 of life.[11] A case series reported 7 preterm neonates with congenital thyrotoxicosis. Mean gestational age was 30 weeks and median birthweight was 1.96 kg. Mean postnatal age at diagnosis was 9 days (range 1-16 days). Six were tachycardic with resting pulse rates in excess of 180 beats/min. Three infants had failed to regain birthweight by day 14 of life and in two, weight failed to increase. Mean age at commencement of antithyroid drugs (ATD) was 12 days ranging from 7 to 26 days. Two infants received PTU alone at a dosage of 6-16 mg/kg/day. Five received carbimazole with starting dosages of 0.25-1.0 mg/kg/day and propranolol (0.5-2.0 mg/kg/day). One infant also required prednisolone at 2 mg/kg/day for 5 days. Four infants were transiently biochemically hypothyroid. They found a rapid decline of FT4 concentrations to the hypothyroid range within 48 h of commencing carbimazole in a set of extremely low birthweight (ELBW) twins. In these 2 infants, withdrawal of carbimazole led to rebound of FT4 levels and a recrudescence of thyrotoxic symptoms and carbimazole was cautiously recommenced. The rapid decline may reflect increased sensitivity to standard doses of ATD in ELBW infants due to little or no thyroid reserve with low levels of iodine and thyroid peroxidase, the prime site of action of ATD. The pharmacokinetics of ATDs may also be altered in sick, premature infants with low rate of degradation and clearance of ATD in ELBW infants.[12] There is a case report of neonatal hyperthyroidism secondary to non-autoimmune hyperthyroidism due to a new activating mutation of the TSHR gene. In this infant, carbimazole was started at 4 weeks of age at a dose of 0.8 mg/kg/day. The dose was adjusted to weight

	and fT3 and FT4 levels and ranged from 0.7-1.4 mg/kg/day. At the time of the reporting carbimazole was still given at 0.7 mg/kg/day and child was 5.9 years of age.[13] **Guidelines** **2017 Canadian expert review** recommended a starting dose of 0.4 mg/kg/day (in 2 divided doses) of methimazole in term neonates with titration of dose every 1-2 weeks. These guidelines acknowledge lack of consensus on starting dose and suggest a range from 0.2-1.0 mg/kg/day in 1-3 divided doses.[1]) **2016 American thyroid association** recommend methimazole in children requiring ATD therapy (Recommendation 59). They noted that methimazole comes in 5- or 10-mg tablets and can be given once daily, even in patients with severe hyperthyroidism. The methimazole dose typically used is 0.2–0.5 mg/kg daily, with a range from 0.1–1.0 mg/kg daily. One approach is to prescribe the following whole tablet or quarter to half tablet doses: infants, 1.25 mg/d; 1–5 years, 2.5–5.0 mg/d; 5–10 years, 5–10 mg/d; and 10–18 years, 10–20 mg/d. With severe clinical or biochemical hyperthyroidism, doses that are 50%–100% higher than the above can be used.[5] **2017 UK expert opinion** recommends carbimazole as the main treatment for thyrotoxic neonate. Carbimazole at a dose of 750 micrograms/kg/dose – as single daily dose until euthyroid status is achieved and then gradually reducing to a maintenance dose of 30% to 60% of the initial dose.[3] **2022 UK expert recommendations** by the same author recommended the dose of 750 micrograms/kg/day in 3 divided doses.[2] **Safety** Side effects of methimazole occur in up to 28% of children. The most common side effects are mild, such as transient elevations of liver enzymes, mild and transient leukopenia, skin rashes, gastrointestinal symptoms, arthralgia, and myalgia. Serious side effects (0.5% of children) include agranulocytosis, liver injury, vasculitis and Stevens-Johnson syndrome. Agranulocytosis most commonly presents with fever, sore throat, or mouth sores. Parents should be instructed to stop ATDs immediately if these occur.[1] **Pharmacokinetics** Carbimazole is rapidly absorbed from the gastrointestinal tract. Carbimazole is completely and rapidly metabolised to methimazole and it is the latter that is responsible for the antithyroid activity of carbimazole. Most is excreted in the urine.[7]
Practice points	Response to carbimazole may be delayed by days to weeks until depletion of thyroid hormone stores [1] and until steady state carbimazole levels are reached (half-life). Hence propranolol 2mg/kg in two divided doses for 1-2 weeks may be required for symptomatic control [1] Lugols iodine and or corticosteroids should be considered in the very thyrotoxic infant (significant cardiovascular and/or hypermetabolic signs).
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