Levothyroxine (Thyroxine) - ORAL

Newborn use only 2021

Alert	Levothyroxine sodium is the International Non-proprietary Name for thyroxine sodium. Three different brands are available: Eutroxsig, Oroxine and Eltroxin. **Eltroxin is not bioequivalent on a same dose basis with Eutroxsig or Oroxine.** Prescribers should not to interchange Eltroxin and Eutroxsig or Oroxine unless a decision has been made to switch products and there is a plan for monitoring TSH levels and review of dose. The patient should be informed of the same.[1, 2]
Indication	Thyroid hormone deficiency
Action	Levothyroxine exerts effects on most organ systems and is particularly important in the development of the central nervous system. Increases the metabolic rate of body tissues. Also involved in the regulation of cell growth and differentiation.
Drug Type	Levothyroxine sodium previously known as thyroxine sodium, is the monosodium salt of the levo-isomer of thyroxine, the principal secretion of the thyroid gland
Trade Name	Eltroxin tablets, Eutroxsig tablets, Oroxine tablets.
Presentation	Eutroxsig and Oroxine tablets: 50 microgram, 75 microgram, 100 microgram, 200 microgram tablets Eltroxin tablets: 25 microgram, 50 microgram, 75 microgram, 100 microgram, 125 microgram, 200 microgram tablets.
Dosage	**Starting dose:** 10 to 15 microgram/kg/dose DAILY.[2] **Maintenance dose:** 8 to 10 microgram/kg/dose DAILY. **Severe congenital hypothyroidism** [free T4 <5 pmol/L] –Start with highest initial dose. Round dose to nearest half or whole tablet where possible, particularly for discharge eg 25 microgram or 50 microgram. **Refer to monitoring section for goals of therapy.**
Route	PO
Maximum Daily Dose	
Preparation	• Oral compounded suspension is <u>not</u> advised. Tablet freshly dispersed in water immediately prior to administration is recommended. Dose to be rounded to the nearest half/whole tablet where possible and disperse/administer using method 1 or 2 below. Tablets can be difficult to quarter with a tablet cutter. • Method 3 is for preparing a 10 microgram/mL dispersion just prior to administration and should only be used for administering small doses where a tablet/tablet portion cannot be used. Method 3 is for inpatient use only. <u>Method 1</u> – round dose to the nearest half or whole tablet: 1. If required, halve tablet using a tablet cutter. 2. Use tablet crusher to crush tablet/tablet portion. 3. Add approximately 1 mL of water (sterile/freshly boiled and cooled) to powder in tablet crusher and mix well. 4. Draw up suspension in oral syringe/dispenser. 5. Rinse tablet cutter with a few drops of water and add to oral syringe/dispenser. Make sure as much as possible of the suspension is transferred to ensure an accurate dose. 6. **Do not allow suspension to settle before administration.** 7. Draw a small amount of air into the oral syringe/dispenser. Administer the contents of the oral syringe/dispenser immediately with the tip pointing down, using the small pocket of air to push all the liquid out of the syringe/oral dispenser. <u>Method 2</u> – round dose to the nearest half or whole tablet: 1. Remove plunger from oral syringe/dispenser. 2. If required, halve or quarter tablet using a tablet cutter.

	3. Place tablet/tablet portion into the barrel of the oral syringe/dispenser and replace the plunger. 4. Draw up 1–5 mL of water (sterile/freshly boiled and cooled) into the syringe. 5. Cap the oral syringe/dispenser and shake until tablet is fully dispersed. This may take up to 2 minutes. 6. **Do not allow suspension to settle before administration.** 7. Draw a small amount of air into the oral syringe/dispenser. Administer the contents of the oral syringe/dispenser immediately with the tip pointing down, using the small pocket of air to push all the liquid out of the syringe/oral dispenser. <u>Method 3</u> – For inpatient use only. Reserve this method for small doses which cannot be rounded to a half or whole tablet: 1. Remove the plunger from a 5 mL oral syringe/dispenser. 2. Place one 50 microgram tablet into the barrel of the oral syringe/dispenser and replace the plunger. 3. Draw up exactly 5 mL of water (sterile/freshly boiled and cooled) into the oral syringe/dispenser. 4. Cap the oral syringe/dispenser and shake until tablet is fully dispersed. This may take up to 2 minutes. 5. The resulting suspension concentration is 10 microgram/mL. 6. **Do not allow suspension to settle before discarding the excess**. 7. Immediately discard any excess from the syringe, leaving only dose to be administered in the syringe (eg if 10 microgram is to be delivered, dispose of 4 mL, leaving only 1 mL in the syringe). 8. Administer the medication immediately, just before a feed.
Administration	Can be administered in the morning or evening, preferably before feed. Should be administered in the same way, at the same time every day. Levothyroxine should not be mixed with substances that interfere with gastrointestinal absorption, such as soy protein formula, concentrated iron or calcium [ensure at least a 2-hour interval].
Monitoring	The goal of initial therapy is to raise free T4 concentration to the upper end of the normal range within 2 weeks of starting therapy and decrease the TSH to <20 mU/L within the first month.[1, 2] The goal of maintenance therapy is to normalise the TSH and aim for free T4 in the upper half of the normal range.[2] The baby is re-examined and repeat thyroid tests are performed at two weeks after starting therapy, at 6 weeks, at 3 months and 2–3-monthly for the first year of life. More frequent review may be necessary if problems arise. Thereafter, clinical examination and thyroid function testing occurs three-monthly unless there has been a significant dose change, a change to or from soy-based formula or there is a clinical indication. Reviews can be done at about four-monthly intervals after the age of three years and in older children four- to six-monthly.[1]
Contraindications	Known hypersensitivity to levothyroxine. Untreated hyperthyroidism. Uncorrected primary or secondary adrenal insufficiency. Acute myocardial infarction.
Precautions	In pre-existing cardiac insufficiency, introduce levothyroxine at 50% of the target replacement dose and increase after 2 weeks based on free T4 levels.
Drug Interactions	Ketamine – Concurrent use may result in marked hypertension and tachycardia. Glucocorticoids – can decrease serum thyroglobulin concentration, affect deiodinase activity, decrease TSH secretion. Ferrous sulphate, calcium carbonate, PPIs, H_2 blockers and bile acid sequestrants can affect levothyroxine absorption. Phenytoin, phenobarbital, carbamazepine – can affect thyroid hormone metabolism therefore increasing levothyroxine requirements. Dopamine, dobutamine, growth hormone – can decrease TSH secretion

	Radioiodine contrast agents and topical iodine application: may lead to transient hypothyroidism associated with low free T4, low free T3 and variable TSH (the Wolff–Chaikoff effect).[3-5]
Adverse Reactions	Uncommon. Too high a replacement dose can cause manifestations of thyrotoxicosis. Overtreatment with levothyroxine may cause craniosynostosis, accelerated growth and maturation, disturbed sleep patterns and effects on temperament. There can also be behavioural problems (social withdrawal, hyperactivity, conduct problems and anxiety) in children treated with initial starting doses of levothyroxine >10 microgram/kg/day. Overtreatment should be avoided by careful monitoring. [2]
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Tablets: discard unused portion.
Storage	Eutroxsig and Oroxine tablets: Store at 2–8°C. Tablets may be stored below 25°C for up to 14 days. Please refer to special comments section for further details. Protect from light. Eltroxin tablets: Store below 25°C. Protect from light.
Special Comments	Milk, calcium, iron, multivitamin supplements – may influence the absorption of levothyroxine. For many years, two levothyroxine preparations have been marketed in Australia, Oroxine and Eutroxsig (both marketed by Aspen Pharmaceuticals), available in 50, 75, 100 and 200 microgram tablets. These preparations are identical, and so it has been immaterial which is dispensed to patients, and brand switching has not been problematic. A new preparation, Eltroxin (also marketed by Aspen) is now available which features a wider range of tablet strengths (25, 50, 75, 100, 125, and 200 microgram) and (unlike Oroxine/Eutroxsig) does not require refrigeration. This may allow more accurate daily dosing for patients and may be more convenient.[6] However, Eltroxin is not bioequivalent on a same dose basis with Eutroxsig/ Oroxine. If a decision is made to switch a patient from Eutroxsig/ Oroxine to Eltroxin, then prescribers should have a plan for monitoring TSH. Prescribers should be aware that dose adjustment may be required. Prescribers should tell their patients not to interchange Eltroxin and Eutroxsig/ Oroxine unless a decision has been made to switch products and there is a plan for monitoring TSH levels and review of dose. [1, 2, 6]
Evidence	**<u>Routine newborn screening</u>** Newborn screening is recommended on all neonates at approximately 2–5 days after birth.[1, 2, 7] In Australasia, the primary screening test for congenital hypothyroidism is a TSH assay. This detects newborns with primary hypothyroidism, but not those with central congenital hypothyroidism who have a normal or low TSH. Conventional newborn screening capillary TSH cut offs (10 to 15 mU/L) fail to detect all infants with congenital hypothyroidism, particularly in sick and very low birthweight or premature infants.[8-10] TSH screening should be repeated in very low birth weight or premature infants a few weeks after the initial specimen to detect those babies where immaturity of the hypothalamic-pituitary- thyroid axis may initially mask primary congenital hypothyroidism. It is recommended that the test be repeated two weeks after birth in babies 1000–1500 g and at four weeks in those <1000 g.[1] **<u>Capillary TSH and free T4 correlation</u>** A <u>newborn screening</u> capillary TSH threshold >40 mU/L has 90.3% sensitivity and 65.9% specificity for predicting a venous fT4 of <10 pmol/L (moderate hypothyroidism), whereas a TSH >20 mU/L has 96% sensitivity and 36% specificity.[11] If the capillary TSH concentration from newborn screening is >40 mU/L whole blood, The European Society for Paediatric Endocrinology recommends starting treatment as soon as a good venous sample can be obtained without waiting for the venous blood test result, unless venous thyroid function test (TFT) results are available on the same day. If capillary TSH concentration is <40 mU/l of whole blood, the clinician may wait for the results of venous TFT, provided that these results are available on the following day.[2] There is also insufficient evidence to determine the accuracy of a heel prick (capillary) TSH and fT4 for diagnosis of congenital hypothyroidism (ie predicting a simultaneously taken venous TSH and free T4). Limited data in school-age Down Syndrome children suggests a capillary sample may

underestimate the venous TSH, although only a single child had a fT4 <10 pmol/L.[12] Conclusion: A venous TSH and fT4 sample is preferred for diagnosis of congenital hypothyroidism.

Replacement therapy for hypothyroidism

The European Society for Paediatric Endocrinology consensus group on congenital hypothyroidism defined the severity of hypothyroidism in terms of fT4 ranges, with <5 pmol/L as severe, 5–10 pmol/L as moderate and 10–15 pmol/L as mild hypothyroidism. The goal of newborn screening for congenital hypothyroidism is to ensure that affected infants start treatment as soon as possible, so that neurological impairment is either prevented or minimised. The European Society for Paediatric Endocrinology (ESPE) consensus states that thyroxine treatment should be started as soon as possible and not later than within the first 2 weeks of life. [2]

The criteria for recall and arrangements for evaluation vary according to country and newborn screening program.[1, 7, 13-16] For TSH levels triggering immediate recall for diagnostic testing, there should be immediate notification by phone to the responsible health team, followed by electronic and printed notification giving details of the mother and baby and screening results.[1, 14] For TSH levels triggering recall for repeat capillary screening, there should be electronic and printed notification giving details of the mother and baby and screening results to enable retesting within 7–10 days.[1, 14] The UK National Screening Committee recommend standards for initiation of treatment for congenital hypothyroidism suspected on initial screening sample by 17 days of age and, for infants suspected on a repeat blood spot sample that follows a borderline TSH, treatment is initiated by 24 days of age.[17]

Higher versus lower dose of thyroxine replacement therapy for hypothyroidism

The Australian Paediatric Endocrine Group guidelines recommend levothyroxine treatment is started as soon as the diagnosis has been confirmed by thyroid function tests (preferably the same day as the evaluation). A recommended starting dose is 10 microgram/kg/day. Dosage needs to be adjusted at follow-up visits with the aim of increasing the free T4 concentration to the upper end of the normal range within 2 weeks of starting therapy and decreasing the TSH to <20 mU/L within the first month.[1]

A systematic review of high versus low dose of initial thyroid hormone replacement for congenital hypothyroidism identified only one RCT evaluating the effects of high (10 to 15 microgram/kg/day) versus low dose (5 to 9.9 microgram/kg/day) of initial thyroid hormone replacement for CHT. [18] The single RCT [19, 20] reported initial dosing of 50 microgram/day (12–17 microgram/kg per day) raised serum T4 and free T4 concentrations to target range by 3 days and normalised TSH by 2 weeks of therapy. Infants commenced on higher initial levothyroxine doses (50 microgram) had full-scale IQ scores 11 points higher than those started on lower (37.5 microgram g) initial doses. However, verbal IQ, performance IQ, and achievement scores did not differ. (LOE II)

A systematic review of controlled studies that reported an association between cognitive outcome, severity of CHT and dosage at start of treatment found 11 studies that reported outcomes on 438 patients with CH: 156 with severe CHT (initial serum T4 ≤2 mg/dL or fT4 ≤3 pmol/L) and 282 with moderate or mild CHT (initial serum T4 >2 mg/dL or fT4 >3 pmol/L) [23–32]. The initial levothyroxine dose was classified as high (>10 microgram /kg), median (8 to 10 microgram /kg) or low (<8 microgram /kg). Patients with severe CH treated with a low initial levothyroxine dose had significantly lower IQ scores than patients with moderate/mild CH (pooled mean difference, 26.0; 95% CI: 29.1, 23.0) as well as patients with severe CH treated with a median levothyroxine dose (pooled mean difference, 29.2; 95% CI: 215.1, 23.3). Only in the subgroup treated with a high initial levothyroxine dose >10 microgram /kg per day was there no significant IQ difference between patients affected by severe CH vs mild/moderate CH. (LOE III – 2) A second systematic review of controlled studies found 17 studies that assessed the starting treatment dose in children with CHT.[21] Although most studies favoured a high initial treatment dose, some studies reported an increased incidence of overtreatment with high-dose thyroxine. In addition, one study reported that although infants

initiated on higher dose levothyroxine had better performances and indexes of intelligence, verbal ability, and memory, they also had more behavioural problems, including increased anxiety, poorer concentration and social withdrawal.[22]

Conclusion: The European Society for Paediatric Endocrinology recommends an initial levothyroxine dose of 10–15 microgram /kg per day. Infants with severe disease, as defined by a very low pretreatment T4 or free T4 concentration, should be treated with the highest initial dose. Overtreatment should be avoided by careful monitoring. [2]

Postnatal thyroid hormones for preterm infants with transient hypothyroxinaemia

A systematic review by Osborn DA et al 2007 found only one eligible study providing insufficient evidence to determine whether use of thyroid hormones for treatment of preterm infants with transient hypothyroxinaemia (low T4, normal TSH) results in changes in neonatal morbidity and mortality or reductions in neurodevelopmental impairments.[23] (LOE I)

Thyroid hormones for preventing neurodevelopmental impairment in preterm infants

A systematic review by Osborn DA 2001 that included 9 studies found no support for the use of thyroid hormones in preterm infants to reduce neonatal mortality, improve neurodevelopmental outcome or to reduce the severity of respiratory distress syndrome. [24] A subgroup analysis of data from one RCT (van Wassenaer 1997) which showed benefits in infants 24–25 weeks gestation was not pre-specified.[25-27]

Conclusion: Prophylactic thyroid hormone supplementation in preterm infants and for treatment of transient hypothyroxinaemia should only be used in the context of an adequately powered clinical trial. (LOE I GOR D)

Replacement therapy in Down syndrome

A single RCT assessed the effect of thyroxine 8 microgram /kg per day in 196 Down Syndrome infants with normal newborn congenital hypothyroidism screening.[28, 29] Thyroxine-treated children had a smaller delay in motor developmental age (−0.7 months, 95% CI −1.4 to 0), but not mental developmental age (−0.7 months, 95% CI −1.5 to 0.2) at 24 months. Levothyroxine-treated children had greater gains in length (1.1 cm, 95% CI 0.2 to 2.0) and weight (378 g, 95% CI 55 to 701). However, at a mean age of 10.7 years, 123 infants were assessed as having no difference in mental or motor development, communication skills or fine-motor coordination. Levothyroxine-treated children had a larger HC (50.4 vs 49.8 cm, P 0.04) and tended to be taller (133.2 vs 131.1 cm, P0.06). The differences were greater in children with TSH ≥5 IU/L (HC: levothyroxine50.5 vs placebo 49.7 cm, P 0.01; height: levothyroxine133.8 vs placebo 130.8 cm, P 0.02), but were not found in children with TSH <5 mIU/L.
Conclusion: Administration of levothyroxine to young children with DS to stimulate general mental or motor development later in life cannot be recommended. However, levothyroxinetreatment may increase growth, especially in children with elevated neonatal plasma TSH concentrations.[28] LOE II GOR D

Thyroid hormones in infants undergoing cardiac surgery

Thyroid hormone has been tested during and after cardiac surgery with the hypothesis that it may enhance cardiac contractility of the uninjured or failing myocardium in situations where thyroid metabolism is impaired. There is a single trial of oral thyroxine in in infants undergoing cardiac surgery [30]. *Talwar et al 2018* in infants undergoing open-heart surgery compared oral thyroxin 5 microgram/kg 12 hours before surgery and once daily for the remainder of ICU stay versus placebo. Oral thyroxin supplementation improves the cardiac index, reduced inotrope requirement, duration of mechanical ventilation, ICU and hospital stay and therapeutic intervention scoring system score.

Pharmacokinetics/pharmacodynamics

Triiodothyronine (T3) is the biologically active hormone, but there is no evidence that combined therapy with levothyroxine and liothyronine is more beneficial than treatment withlevothyroxine alone, probably due to the high degree of efficiency of endogenous deiodinases which break T4 down

	into T3.[2] levothyroxine is available in tablet but not licensed as a liquid form in Australia. Liquid preparations may be better absorbed, particularly in patients with malabsorption and in newborn infants in whom lower TSH levels were reported.[31-31] Suspensions prepared by pharmacists may not allow reliable dosing.[2] Brand and generic levothyroxine are not bioequivalent so it is prudent to use a brand preparation, particularly in severe cases.[2, 34] Peak concentrations occur 2 to 4 hours after oral administration. Therefore blood for thyroid function tests should preferably be taken immediately before a dose is due [1]. Fasting will increase the extent of absorption, whereas malabsorption may decrease absorption. The daily levothyroxine tablet should be crushed and mixed with water, expressed breast milk, or formula. Although it is recommended to administer levothyroxine on an empty stomach and avoid food for 30–60 min, this is not practical in an infant. levothyroxine should not be mixed with substances that interfere with gastrointestinal absorption, such as soy protein formula, concentrated iron, or calcium.[16] Levothyroxine sodium is variably but adequately absorbed from the gastrointestinal tract following oral administration. Approximately 50 to 80% of levothyroxine sodium is absorbed.[2] Elimination half-life is about 6–7 days.[35, 36] Commencing thyroxine 10 to 15 microgram/kg/day will normalise serum free T4 or T4 in 3 days and TSH in 2 to 4 weeks following the initiation of therapy.[16]
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Authors Contribution

Original author/s	Ansar Kunjunju, Srinivas Bolisetty
Evidence Review - original	David Osborn
Updated evidence review	David Osborn
Expert review	Shihab Hameed, Amy Thorby-Lister, Kristen Neville, Jan Walker, Irene Mitchelhill
Nursing Review	Eszter Jozsa
Pharmacy Review	Jing Xiao, Cindy Chen, Carmen Burman, Branko Radojkovic
ANMF Group contributors	Nilkant Phad, Himanshu Popat, Victor Sam Rajadurai, Roland Broadbent
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty