

LIOTHYRONINE (Triiodothyronine)

Newborn use only

2018

Alert	NOT a choice for maintenance thyroid replacement due to its short duration of action. Liothyronine is to be used only after consultation with and approval from a paediatric endocrinologist. Intravenous liothyronine is available in Australia only via the Special Access Scheme.
Indication	<ol style="list-style-type: none">Hypothyroidism (high TSH and low T₄/T₃, or low T₄/T₃ alone if hypopituitarism) in whom oral levothyroxine is contraindicated for a prolonged period e.g. following bowel surgery.Sick euthyroidism (low T₄/T₃ with no significant elevation of TSH), particularly after cardiac surgery – consider treatment if free T₃ concentration is <1.5 picomol/L or if free T₃ is <3.5 picomol/L and inotropic support or haemodynamic instability is present.(2, 6-14)
Action	The principal pharmacological effect of exogenous thyroid hormones is to increase the metabolic rate of body tissues. The biological action of liothyronine (L-T ₃) is qualitatively similar to that of levothyroxine (T ₄) but the effect develops in a few hours and disappears within 24–48 hours of stopping treatment.
Drug Type	Liothyronine is a synthetic form of triiodothyronine (T ₃), a thyroid hormone.
Trade Name	IV: Thyrotardin (Medsurge, UK) or Triostat-R (Mercury Pharma, UK) can be obtained via the Special Access Scheme.
Presentation	IV Thyrotardin 100 microgram vial. Triostat-R 20 microgram vial. Contains dextran 110 and sodium hydroxide as excipients.
Dosage/Interval	IV continuous infusion 0.05 microgram/kg/hour (range 0.05–0.15 microgram/kg/hour [titrated to free T ₃ of 4.5 to 7.8 picomol/L in neonates and 5.2–8.0 picomol/L in 31–60 days old and 4.1–7.9 picomol/L in 61 days–12 months]) [1]]. May be given centrally or peripherally, for up to 72 hours – or until free T ₃ is normal. IV slow bolus injection 0.4 microgram/kg over 20 minutes. Subsequent doses 0.2 microgram/kg over 20 minutes every 3 to 12 hours (titrated to free T ₃ level – normal is 4.5 to 7.8 picomol/L in neonates [1] and 2.3 to 9.2 picomol/L in 1 month to 7 years of age [28]). Discontinuing intravenous T₃ treatment <ul style="list-style-type: none">In infants with sick euthyroid syndrome in whom T₃ treatment has been started as an adjunct to inotropic support, intravenous T₃ therapy can be weaned over 24 hours or simply stopped once inotropic support is no longer required.Intravenous T₃ can typically be ceased when FT₃ levels reach the normal range.If hypothyroidism is expected to be an on-going problem, the infant should be started on oral levothyroxine (T₄) treatment as soon as possible. Levothyroxine should commence before T₃ is discontinued. Intravenous T₃ can only be stopped when T₄ concentrations are within the normal range (10–20 picomol/L). This may take a few days.
Route	IV
Maximum Daily Dose	
Preparation/Dilution	IV Bolus: Add 2mL of water for injection to 20 microgram vial to make 10microgram/mL solution. Shake gently to dissolve. Further dilute 2mL of reconstituted solution (20 micrograms) with 18mL of sodium chloride 0.9% giving a concentration of 1 microgram/mL.* IV Infusion: Add 4mL of water for injection to 20 microgram vial to make 5microgram/mL solution. Shake gently to dissolve. Further dilute 1 mL of reconstituted solution (5 micrograms) to make up to 50 mL of sodium chloride 0.9% giving a concentration of 0.1 microgram/mL. *Note that this product is irritant to veins (alkaline).
Administration	IV slow bolus injection over 20 minutes. IV continuous infusion: Use a light-resistant, low absorbing, non-PVC extension set. Liothyronine (T ₃) is only stable for 24 hours, the giving set and drug need to be changed every

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	24 hours.
Monitoring	<p>Reverse T₃ (as well as TSH, T₃ and T₄) is to be measured on all patients before starting therapy.</p> <p>In infants in whom a T₃ infusion is required, the aim is to titrate the infusion rate to achieve a normal plasma concentration of free T₃ (titrated to free T₃ of 4.5 to 7.8 picomol/L in neonates, 5.2–8.0 picomol/L in 31–60 days old and 4.1–7.9 picomol/L in 61 days–12 months).</p> <p>During therapy, free T₃ should be measured and reviewed regularly.</p> <p>Continuous cardiac monitoring for IV infusion to watch for tachycardia and arrhythmias as signs of possible overdose.</p>
Contraindications	<p>Hypersensitivity to liothyronine sodium.</p> <p>Patients with untreated hyperthyroidism.</p>
Precautions	<p>Patients with cardiovascular disorders.</p> <p>Patients with untreated adrenal cortical insufficiency.</p>
Drug Interactions	<p>Anticoagulants: Liothyronine sodium therapy may potentiate the action of anticoagulants by increasing the catabolism of vitamin K-dependent clotting factors.</p> <p>Anticonvulsants: Initiation or discontinuation of anticonvulsant therapy may alter liothyronine dose requirements. Phenytoin concentrations may be increased by liothyronine.</p> <p>Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of thyroid hormones and may displace them from plasma proteins.</p> <p>Cardiac glycosides: Thyroid hormones may potentiate digitalis toxicity. The increased metabolic rate following liothyronine therapy may increase digitalis requirements.</p> <p>Cholestyramine: Reduces gastrointestinal absorption of liothyronine by binding liothyronine within the gut lumen.</p> <p>Catecholamines: Liothyronine increases receptor sensitivity to catecholamines, thus potentially increasing the risk of cardiac arrhythmias.</p> <p>Ketamine: May cause hypertension and tachycardia when administered to patients receiving thyroid replacement therapy.</p> <p>Insulin or oral hypoglycaemics: Requirements of insulin or oral hypoglycaemics may increase in patients receiving therapy with liothyronine.</p> <p>Amiodarone and iodinated contrast media can, due to its high iodine content, cause both hyperthyroidism and hypothyroidism. Dose adjustment of liothyronine may be necessary.</p> <p>Enzyme-inducing drugs, barbiturates, rifampicin, carbamazepine and other drugs with hepatic enzyme properties, can increase the hepatic clearance of liothyronine.</p>
Adverse Reactions	<p>Tachycardia, tachyarrhythmia, hypertension.</p> <p>Overtreatment may cause hyperactivity, bone-age advancement and craniosynostosis.</p> <p>Excessive dosage may also cause diarrhoea, ischaemic cardiac pain, sweating, muscle cramps and muscle weakness.</p> <p>Late-onset circulatory collapse has been reported in preterm infants treated with thyroid hormones particularly in the context of cortisol insufficiency.</p>
Compatibility	<p>In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.</p>
Incompatibility	<p>In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.</p>
Stability	<p>IV: Thyrotardin – Shelf life at 2–8°C is 4 years. The reconstituted solution should be used immediately.</p> <p>IV: Triostat-R – Use immediately after reconstitution.</p>
Storage	<p>IV</p> <p>Thyrotardin is to be stored in a refrigerator between 2 and 8°C. Protect from light. The reconstituted solution must be protected from direct sunlight.</p> <p>Triostat-R: Do not store above 25°C. Protect from light.</p>
Special Comments	

<p>Evidence summary</p>	<p>Hypothyroidism <u>Liothyronine is the synthetic form of T₃ and, although usually administered IV, it may also be administered enterally; but absorption may be less predictable.</u></p> <p>T₄ can be considered as the prohormone of T₃ and is converted to active T₃ by deiodination. About 80% of circulating T₃ is produced by this conversion in the liver and other tissues, except the cardiac myocyte; the remaining 20% is secreted directly by the thyroid. T₃ and T₄ are carried in the circulation bound to thyroxine-binding globulin (TBG), transthyretin and albumin, and exert a negative feedback on the release of TSH and TRH.[2]</p> <p>Triiodothyronine for hypothyroidism: No report was found of use of liothyronine alone for treatment of congenital hypothyroidism or hypothyroidism of other causes.</p> <p>Triiodothyronine in addition to levothyroxine for hypothyroidism: In a small RCT (n = 14) of infants with congenital hypothyroidism, triiodothyronine plus levothyroxine treatment resulted in slower TSH normalisation compared to levothyroxine alone. [29]</p> <p>Conclusion: There is insufficient evidence to support the use of liothyronine alone or in combination with levothyroxine for treatment of congenital hypothyroidism or hypothyroidism of other causes.</p> <p>In adults, two systematic reviews found combined T₄ and T₃ treatment does not improve well-being, cognitive function or quality of life compared with T₄ alone. T₄ alone may be beneficial in improving psychological or physical well-being. According to the current evidence, T₄ alone replacement may remain the drug of choice for hypothyroid patients.[3, 4] (Adults LOE I GOR B)</p> <p>Recommendation: The European Thyroid Association guidelines, 2012 concluded there is insufficient evidence that T₄ + T₃ combination therapy is better than T₄ monotherapy, and it is recommended that T₄ monotherapy remain the standard treatment of hypothyroidism. T₄ + T₃ combination therapy should be considered solely as an experimental treatment modality.[5]</p> <p>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. Several RCTs have assessed the effect of liothyronine in infants and children undergoing cardiac surgery.[6-13] A systematic review, updated in 2010, concluded there is a lack of evidence concerning the effects of triiodothyronine supplementation in infants undergoing cardiac surgery.[14] Individual trials reported on different doses and variable clinical effects.</p> <p>Triiodothyronine trials: Several RCTs have assessed the effect and safety of T₃ for infants undergoing cardiac surgery. <i>Bettendorf et al 2000</i> in 40 children aged 2 days to 10 years undergoing cardiac surgery compared a daily infusion of triiodothyronine 2 microgram/kg on day 1 after surgery then 1 microgram/kg daily until 12 days after surgery with placebo [1]. In all patients, postoperative plasma concentrations of TSH, T₄, free T₄ and T₃ were abnormally low and plasma concentrations of reverse T₃ were raised. After start of treatment, T₃ was significantly higher in patients given T₃ whereas TSH, T₄, free T₄ and rT₃ remained similar. Infants given T₃ had a higher mean cardiac index, improved systolic cardiac function (particularly in patients with longer cardiopulmonary bypass operations) and had lower mean treatment scores. <i>Portman et al 2000</i> in 14 infants <1 year age undergoing VSD or tetralogy of Fallot repair assessed IV 0.4 microgram/kg immediately before the start of cardiopulmonary bypass and again with myocardial reperfusion.[12] T₃ and FT₃ were maintained, heart rate was</p>
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transiently elevated and peak systolic pressure-rate product was increased after 6 hours. *Chowdhury et al 2001*, in 75 patients aged from birth to 18 years undergoing cardiac surgery, compared a continuous T₃ infusion 0.05–0.15 microgram/kg/hour to no treatment to maintain serum T₃ within the normal range.[11] Infants had normalised serum T₃ concentrations and reduced use of inotropes in the neonatal strata only. There was no difference in mechanical ventilation or duration of stay. *Mackie et al 2005*, in 42 infants undergoing a Norwood procedure or two-ventricle repair of interrupted aortic arch and VSD, used a continuous T₃ infusion 0.05 microgram/kg/hour.[10] T₃ and free-T₃ were increased above baseline, negative fluid balance was attained more rapidly but cardiac index did not change. There was no difference in ECMO use, extubation time or mortality. *Portman et al 2010*, in 193 children <2 years old undergoing heart surgery with cardiopulmonary bypass, compared a bolus of 0.4 microgram/kg immediately before CPB, 0.4 microgram/kg on the release of the aortic cross-clamp, and then 0.2 microgram/kg at 3, 6, and 9 hours after cross-clamp release.[9] Overall, treatment did not reduce extubation time. There were no significant differences between T₃ and placebo for heart rate, mean arterial blood pressure or mean arterial blood pressure times heart rate over the first 24 hours. The inotropic scores were not significantly different. Age stratification found T₃ supplementation reduced extubation time for infants <5 months but increased it for infants ≥5 months. *Marwali et al 2013*, in infants <2 years of age undergoing congenital heart surgery, assessed oral T₃ 0.5 microgram/kg every 12 hours versus placebo [7]. Total and free triiodothyronine levels were maintained within normal limits. There was no difference in cardiovascular or clinical outcomes. *Marwali et al 2017*, in infants <3 years age undergoing congenital heart surgery, assessed oral T₃ 1.0 microgram/kg or placebo by nasogastric tube every 6 hours for 60 hours after induction of anesthesia [6]. TSH was suppressed in the T₃ group during treatment. There was a marginal decrease in extubation time in the T₃ group and significantly more sepsis in the placebo group. **Conclusion:** In infants undergoing cardiac surgery, particularly those with low T₃, there is some evidence that T₃ administration improves cardiac function and reduces inotrope and treatment needs, particularly in infants <5 months age. It is unclear whether there are significant improvements in morbidity or duration of care.

Thyroxine trial: *Talwar et al 2018*, in infants undergoing open-heart surgery, compared oral levothyroxine 5 microgram/kg 12 hours before surgery and once daily for the remainder of ICU stay versus placebo [15]. Oral levothyroxine supplementation improved the cardiac index, reduced inotrope requirement, decreased duration of mechanical ventilation, ICU and hospital stay and the therapeutic intervention scoring system score.

Recommendation: The Pediatric Cardiac Intensive Care Society 2014 Consensus Statement reported studies suggest a positive outcome of normalising T₃ levels acutely in newborns after cardiac surgery. However, they concluded adequately powered studies are needed before a uniform recommendation can be made. Until then, therapeutic decisions should be made based on individual circumstances, taking into account the severity of the T₃ deficiency, as well as the symptoms that might be attributable to thyroid dysfunction (e.g. bradycardia, hypothermia and increased SVR), and in consultation with paediatric endocrinology[2]. [LOE I GOR D]

Triiodothyronine for prevention or treatment of hypothyroxinaemia: No study has reported the effect of liothyronine in preterm infants with transient hypothyroxinaemia (normal TSH, low T₄).

Triiodothyronine for prevention or treatment of respiratory distress: Systematic review found

2 studies that enrolled preterm infants with respiratory distress.[16] *Amato et al 1988* allocated infants to levothyroxine 50 microgram/dose at 1 and at 24 hours or to no treatment. *Amato et al 1989* allocated infants to triiodothyronine 50 microgram/day in two divided doses for two days or to no treatment.[17] Neither study reported any significant benefits in neonatal morbidity or mortality from use of thyroid hormones. There is no evidence from controlled clinical trials that postnatal thyroid hormone treatment reduces the severity of respiratory distress syndrome, neonatal morbidity or mortality in preterm infants with respiratory distress syndrome.[16] (LOE II GOR C)

Prophylactic triiodothyronine in preterm infants: A systematic review of prophylactic thyroid hormones in preterm infants to reduce neonatal mortality, neonatal morbidity or improve neurodevelopmental outcomes [18] found four studies enrolling 318 infants, with a single study (Valerio 2004) that reported the effect a single dose of triiodothyronine 0.5 microgram/kg at 24 hours then levothyroxine 8 microgram/kg/day for 6 weeks versus levothyroxine alone versus placebo. Overall, the review found no evidence that prophylactic thyroid hormones in preterm infants reduced neonatal mortality, neonatal morbidity or improved neurodevelopmental outcomes. *Valerio et al 2004* reported no effect of T₃ 0.5 microgram/kg on the cardiovascular system. The review does not support the use of prophylactic thyroid hormones in preterm infants.[18] [LOE I GOR D] A second trial in infants 24 to 27 weeks gestation compared placebo vehicle versus glucose 5% versus potassium iodide 30 microgram/kg/day versus continuous daily infusions of either 4 or 8 microgram/kg/day of T₄ for 42 days versus bolus daily infusions of either 4 or 8 microgram/kg/d of T₄. T₄ was accompanied by T₃ 1 microgram/kg/day during the first 14 postnatal days. Combined T₄ and T₃ treatment resulted in suppression of TSH to <0.4 mIU/L in >80%. [19]

Conclusion: There is no evidence of benefit from prophylactic thyroid hormones in preterm infants. Combined T₄ (4 or 8 microgram/kg/day) and T₃ (1 microgram/kg/day) treatment resulted in excessive suppression of TSH.

Prophylactic triiodothyronine and hydrocortisone in preterm infants: A single trial in 253 infants born <30 weeks gestation compared routine hydrocortisone 1 mg/kg and T₃ 6 microgram/kg versus placebo. [20] No beneficial effects of T₃ and hydrocortisone were shown. Although FT₃ concentrations were doubled by the treatment infusion, FT₄ was significantly suppressed.

Pharmacokinetics:

The bioavailability of enteral levothyroxine is erratic ranging from 40% to 80% and dependent on dosage form and the presence of food. When administered in a fasting state, the bioavailability can be increased by about 20%. Time to peak occurs at 2 hours post-administration. Conversely, enteral liothyronine (T₃) bioavailability is 85–95%. Levothyroxine is over 99% protein bound to plasma proteins, such as albumin, TBG and transthyretin. Levothyroxine is deiodinated and metabolised to T₃ in the blood, liver, kidney and many other tissues. In addition, levothyroxine is metabolised through glucuronidation, conjugation and enterohepatic recirculation. Liothyronine is further metabolised in the liver to inactive metabolites. The onset of action of T₃ is within a few hours, peaking at 48–72 hours and duration of action up to 72 hours.

The half-life of T₄ reported in adults is much longer than that of T₃, approximately 1.5–2 days compared with 7 hours, respectively. [2]

Safety: In the context of clinical trials of T₃ there have been few reported adverse events. [6, 7, 9-12] Thyroid hormone treatment in newborn infants has been associated with late onset circulatory collapse [21] which has also been associated with concomitant cortisol deficiency. [22] Overtreatment may cause hyperactivity, bone age advancement and craniosynostosis. There are case reports of premature craniosynostosis [23] and pseudotumour cerebri [24] with thyroid hormone treatment. Long-term levothyroxine treatment in young adults with

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	<p>congenital hypothyroidism has been associated with impaired diastolic function and exercise capacity and increased intima-media thickness [25]. In patients on long-term levothyroxine therapy, those with a high or suppressed TSH had an increased risk of cardiovascular disease, dysrhythmias and fractures, whereas patients with a low but unsuppressed TSH did not. [26]</p>
References	<ol style="list-style-type: none">1. Strich D, Edri S, Gillis D. Current normal values for TSH and FT3 in children are too low: evidence from over 11,000 samples. <i>J Pediatr Endocrinol Metab.</i> 2012;25:245-8.2. Soto-Rivera CL, Agus MS, Sawyer JE, Macrae DJ. Pediatric Cardiac Intensive Care Society 2014 Consensus Statement: Pharmacotherapies in Cardiac Critical Care Hormone Replacement Therapy. <i>Pediatr Crit Care Med.</i> 2016;17:S59-68.3. Chao M, Jiawei X, Xia H, Guoming W, Yangang W, Xufu W, Shuyao Z. Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. <i>Nuclear Medicine Communications.</i> 2009;30:586-93.4. Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L. Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: Meta-analysis of randomized controlled trials. <i>Journal of Clinical Endocrinology and Metabolism.</i> 2006;91:2592-9.5. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. <i>Eur Thyroid J.</i> 2012;1:55-71.6. Marwali EM, Boom CE, Budiwardhana N, Fakhri D, Roebiono PS, Santoso A, Sastroasmoro S, Slee A, Portman MA. Oral Triiodothyronine for Infants and Children Undergoing Cardiopulmonary Bypass. <i>Ann Thorac Surg.</i> 2017;104:688-95.7. Marwali EM, Boom CE, Sakidjan I, Santoso A, Fakhri D, Kartini A, Kekalih A, Schwartz SM, Haas NA. Oral triiodothyronine normalizes triiodothyronine levels after surgery for pediatric congenital heart disease. <i>Pediatric Critical Care Medicine.</i> 2013;14:701-8.8. Priest JR, Slee A, Olson AK, Ledee D, Morrish F, Portman MA. Triiodothyronine supplementation and cytokines during cardiopulmonary bypass in infants and children. <i>J Thorac Cardiovasc Surg.</i> 2012;144:938-43.e2.9. Portman MA, Slee A, Olson AK, Cohen G, Karl T, Tong E, Hastings L, Patel H, Reinhartz O, Mott AR, Mainwaring R, Linam J, Danzi S, Investigators T. Triiodothyronine Supplementation in Infants and Children Undergoing Cardiopulmonary Bypass (TRICC): a multicenter placebo-controlled randomized trial: age analysis. <i>Circulation.</i> 2010;122:S224-33.10. Mackie AS, Booth KL, Newburger JW, Gauvreau K, Huang SA, Laussen PC, DiNardo JA, del Nido PJ, Mayer JE, Jr., Jonas RA, McGrath E, Elder J, Roth SJ. A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. <i>J Thorac Cardiovasc Surg.</i> 2005;130:810-6.11. Chowdhury D, Djamaa K, Parnell VA, McMahon C, Sison CP, Klein I. A prospective randomized clinical study of thyroid hormone treatment after operations for complex congenital heart disease. <i>Journal of Thoracic and Cardiovascular Surgery.</i> 2001;122:1023-5.12. Portman MA, Fearneyhough C, Ning XH, Duncan BW, Rosenthal GL, Lupinetti FM. Triiodothyronine repletion in infants during cardiopulmonary bypass for congenital heart disease. <i>Journal of Thoracic and Cardiovascular Surgery.</i> 2000;120:604-8.13. Bettendorf M, Schmidt KG, Grulich-Henn J, Ulmer HE, Heinrich UE. Tri-iodothyronine treatment in children after cardiac surgery: A double-blind, randomised, placebo-controlled study. <i>Lancet.</i> 2000;356:529-34.14. Dimmick S, Badawi N, Randell T. Thyroid hormone supplementation for the prevention of morbidity and mortality in infants undergoing cardiac surgery. <i>Cochrane database of systematic reviews (Online).</i> 2004:CD004220.15. Talwar S, Bhoje A, Khadagawat R, Chaturvedi P, Sreenivas V, Makhija N, Sahu M, Choudhary SK, Airan B. Oral thyroxin supplementation in infants undergoing cardiac surgery: A double blind placebo controlled randomized clinical trial. <i>Journal of Thoracic and Cardiovascular Surgery.</i> 2018.16. Osborn DA, Hunt RW. Postnatal thyroid hormones for respiratory distress syndrome in preterm infants. <i>Cochrane Database Syst Rev.</i> 2007:CD005946.17. Amato M, Guggisberg C, Schneider H. Postnatal triiodothyronine replacement and

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