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	1. Hypothyroidism (high TSH and low T_4/T_3, or low T_4/T_3 alone if hypopituitarism) in whom oral levothyroxine is contraindicated for a prolonged period e.g. following bowel surgery. 2. Sick euthyroidism (low T_4/T_3 with no significant elevation of TSH), particularly after cardiac surgery – consider treatment if free T_3 concentration is <1.5 picomol/L or if free T_3 is <3.5 picomol/L and inotropic support or haemodynamic instability is present [1].
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 [2]). **Discontinuing intravenous T_3 treatment** • In infants with sick euthyroid syndrome in whom T_3 treatment has been started as an adjunct to inotropic support, intravenous T_3 therapy can be weaned over 24 hours or simply stopped once inotropic support is no longer required. • Intravenous T_3 can typically be ceased when FT_3 levels reach the normal range. • If hypothyroidism is expected to be an on-going problem, the infant should be started on oral levothyroxine (T_4) treatment as soon as possible. Levothyroxine should commence before T_3 is discontinued. Intravenous T_3 can only be stopped when T_4 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 24 hours.
Monitoring	Reverse T_3 (as well as TSH, T_3 and T_4) is to be measured on all patients before starting therapy. In infants in whom a T_3 infusion is required, the aim is to titrate the infusion rate to achieve a normal plasma concentration of free T_3 (titrated to free T_3 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). During therapy, free T_3 should be measured and reviewed regularly. Continuous cardiac monitoring for IV infusion to watch for tachycardia and arrhythmias as signs of possible overdose.
Contraindications	Hypersensitivity to liothyronine sodium. Patients with untreated hyperthyroidism.
Precautions	Patients with cardiovascular disorders. Patients with untreated adrenal cortical insufficiency.
Drug Interactions	Anticoagulants: Liothyronine sodium therapy may potentiate the action of anticoagulants by increasing the catabolism of vitamin K-dependent clotting factors. Anticonvulsants: Initiation or discontinuation of anticonvulsant therapy may alter liothyronine dose requirements. Phenytoin concentrations may be increased by liothyronine. Anticonvulsants such as carbamazepine and phenytoin enhance the metabolism of thyroid hormones and may displace them from plasma proteins. Cardiac glycosides: Thyroid hormones may potentiate digitalis toxicity. The increased metabolic rate following liothyronine therapy may increase digitalis requirements. Cholestyramine: Reduces gastrointestinal absorption of liothyronine by binding liothyronine within the gut lumen. Catecholamines: Liothyronine increases receptor sensitivity to catecholamines, thus potentially increasing the risk of cardiac arrhythmias. Ketamine: May cause hypertension and tachycardia when administered to patients receiving thyroid replacement therapy. Insulin or oral hypoglycaemics: Requirements of insulin or oral hypoglycaemics may increase in patients receiving therapy with liothyronine. Amiodarone and iodinated contrast media can, due to its high iodine content, cause both hyperthyroidism and hypothyroidism. Dose adjustment of liothyronine may be necessary. Enzyme-inducing drugs, barbiturates, rifampicin, carbamazepine and other drugs with hepatic enzyme properties, can increase the hepatic clearance of liothyronine.
Adverse Reactions	Tachycardia, tachyarrhythmia, hypertension. Overtreatment may cause hyperactivity, bone-age advancement and craniosynostosis. Excessive dosage may also cause diarrhoea, ischaemic cardiac pain, sweating, muscle cramps and muscle weakness. Late-onset circulatory collapse has been reported in preterm infants treated with thyroid hormones particularly in the context of cortisol insufficiency.
Compatibility	In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Incompatibility	In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Stability	IV: Thyrotardin – Shelf life at 2–8°C is 4 years. The reconstituted solution should be used immediately. IV: Triostat-R – Use immediately after reconstitution.
Storage	**IV** 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. Triostat-R: Do not store above 25°C. Protect from light.

Special Comments	
Evidence summary	**Hypothyroidism** Liothyronine is the synthetic form of T_3 and, although usually administered IV, it may also be administered enterally; but absorption may be less predictable. T_4 can be considered as the prohormone of T_3 and is converted to active T_3 by deiodination. About 80% of circulating T_3 is produced by this conversion in the liver and other tissues, except the cardiac myocyte; the remaining 20% is secreted directly by the thyroid. T_3 and T_4 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 [3]. **Triiodothyronine for hypothyroidism:** No report was found of use of liothyronine alone for treatment of congenital hypothyroidism or hypothyroidism of other causes. **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 [4]. **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. In adults, two systematic reviews found combined T_4 and T_3 treatment does not improve well-being, cognitive function or quality of life compared with T_4 alone. T_4 alone may be beneficial in improving psychological or physical well-being. According to the current evidence, T_4 alone replacement may remain the drug of choice for hypothyroid patients [5, 6]. (Adults LOE I GOR B) **Recommendation:** The European Thyroid Association guidelines, 2012 concluded there is insufficient evidence that T_4 + T_3 combination therapy is better than T_4 monotherapy, and it is recommended that T_4 monotherapy remain the standard treatment of hypothyroidism. T_4 + T_3 combination therapy should be considered solely as an experimental treatment modality [7]. **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 [8-14]. A systematic review, updated in 2010, concluded there is a lack of evidence concerning the effects of triiodothyronine supplementation in infants undergoing cardiac surgery [15]. Individual trials reported on different doses and variable clinical effects. **Triiodothyronine trials:** Several RCTs have assessed the effect and safety of T_3 for infants undergoing cardiac surgery. *Bettendorf et al 2000* 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 [8]. In all patients, postoperative plasma concentrations of TSH, T_4, free T_4 and T_3 were abnormally low and plasma concentrations of reverse T_3 were raised. After start of treatment, T_3 was significantly higher in patients given T_3 whereas TSH, T_4, free T_4 and rT_3 remained similar. Infants given T_3 had a higher mean cardiac index, improved systolic cardiac function (particularly in patients with longer cardiopulmonary bypass operations) and had lower mean treatment scores. *Portman et al 2000* 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]. T_3 and FT_3 were maintained, heart rate was 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 T_3 infusion 0.05–0.15 microgram/kg/hour to no treatment to maintain serum T_3 within the normal range [9]. Infants had normalised serum T_3 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 T_3 infusion 0.05 microgram/kg/hour [10]. T_3 and free-T_3 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 [13]. Overall, treatment did not reduce extubation time. There were no significant differences between T_3 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 T_3 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 T_3 0.5 microgram/kg every 12 hours versus placebo [16]. 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 T_3 1.0 microgram/kg or placebo by nasogastric tube every 6 hours for 60 hours after induction of anaesthesia [11]. TSH was suppressed in the T_3 group during treatment. There was a marginal decrease in extubation time in the T_3 group and significantly more sepsis in the placebo group. **Conclusion:** In infants undergoing cardiac surgery, particularly those with low T_3, there is some evidence that T_3 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.

Recommendation: The Pediatric Cardiac Intensive Care Society 2014 Consensus Statement reported studies suggest a positive outcome of normalising T_3 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 T_3 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[3]. [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 T_4).

Triiodothyronine for prevention or treatment of respiratory distress: Systematic review found 2 studies that enrolled preterm infants with respiratory distress [17]. *Amato et al 1988* allocated infants to levothyroxine 50 microgram/dose at 1 and at 24 hours or to no treatment [18]. *Amato et al 1989* allocated infants to triiodothyronine 50 microgram/day in

two divided doses for two days or to no treatment [19]. 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 [17]. (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 [20] 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 [21]. 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 T_3 0.5 microgram/kg on the cardiovascular system. The review does not support the use of prophylactic thyroid hormones in preterm infants [21]. [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 T_4 for 42 days versus bolus daily infusions of either 4 or 8 microgram/kg/d of T_4. T_4 was accompanied by T_3 1 microgram/kg/day during the first 14 postnatal days. Combined T_4 and T_3 treatment resulted in suppression of TSH to <0.4 mIU/L in >80% [22].
Conclusion: There is no evidence of benefit from prophylactic thyroid hormones in preterm infants. Combined T_4 (4 or 8 microgram/kg/day) and T_3 (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 T_3 6 microgram/kg versus placebo [23]. No beneficial effects of T_3 and hydrocortisone were shown. Although FT_3 concentrations were doubled by the treatment infusion, FT_4 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 (T_3) 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 T_3 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 T_3 is within a few hours, peaking at 48–72 hours and duration of action up to 72 hours.
The half-life of T_4 reported in adults is much longer than that of T_3, approximately 1.5–2 days compared with 7 hours, respectively [7].

Safety: In the context of clinical trials of T_3 there have been few reported adverse events [7, 9-14, 16]. Thyroid hormone treatment in newborn infants has been associated with late onset circulatory collapse [24] which has also been associated with concomitant cortisol deficiency [25]. Overtreatment may cause hyperactivity, bone age advancement and craniosynostosis. There are case reports of premature craniosynostosis [26] and pseudotumour cerebri [27] with thyroid hormone treatment. Long-term levothyroxine treatment in young adults with congenital hypothyroidism has been associated with impaired diastolic function and exercise capacity and increased intima-media thickness [28]. 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 [29].
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Authors Contribution

Original author/s	David Osborn, Srinivas Bolisetty
Current version author/s	David Osborn, Srinivas Bolisetty
Evidence Review	David Osborn
Expert review	Shihab Hameed, Ann Maguire, Amy Thorby-Lister, Kristen Neville, Jan Walker
Nursing Review	Eszter Jozsa, Robyn Richards, Kirsty Minter
Pharmacy Review	Jing Xiao, Cindy Chen, Mohammad Irfan Azeem
ANMF Group contributors	Nilkant Phad, Himanshu Popat
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty