Indirect iodine supplementation, by addition of potassium iodate to the water used to irrigate crops, has been tried in areas of iodine deficiency where other methods had proved difficult to implement.[13]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the Committee on Medical Aspects of Food Policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington DC: National Academy Press, 2001. Also available at: http://www.nap.edu/openbook.php?isbn=0309072794 (accessed 21/07/08)
3. WHO. Iodine. In *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 49–71.
4. ICCIDD/UNICEF/WHO. *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination*. Geneva: WHO, 2001. Also available at: http://www.who.int/nutrition/publications/en/idd_assessment_monitoring_elimination.pdf (accessed 01/08/08)
5. WHO. Iodine status worldwide: WHO Global Database on Iodine Deficiency. Geneva: WHO, 2004. Also available at: http://whqlibdoc.who.int/publications/2004/9241592001.pdf (accessed 18/05/05)
6. Delange F, Lecomte P. Iodine supplementation: benefits outweigh risks. *Drug Safety* 2000; **22:** 89–95.
7. Ingenbleek Y, *et al*. Iodised rapeseed oil for eradication of severe endemic goitre. *Lancet* 1997; **350:** 1542–5.
8. Untoro J, *et al*. Efficacy of different types of iodised oil. *Lancet* 1998; **351:** 752–3.
9. WHO. *WHO model formulary*. Geneva: WHO, 2004.
10. Angermayr L, Clar C. Iodine supplementation for preventing iodine deficiency disorders in children. Available in The Cochrane Database of Systemic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 18/05/05).
11. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; **74:** 101–8.
12. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; **74:** 1–3.
13. Cao X-Y, *et al*. Iodination of irrigation water as a method of supplying iodine to a severely iodine-deficient population in Xinjiang, China. *Lancet* 1994; **344:** 107–10.

Radiation protection. Giving a radiologically stable form of iodine to saturate the thyroid gland confers thyroid protection from iodine radionuclides.[1,2] When thyroid protection from a *medical procedure* involving radio-iodine is needed 100 to 150 mg of iodide as potassium iodide may be given orally 24 hours before the procedure and daily for up to 10 days following it.

In the event of a *nuclear accident* authorities in the USA recommend[1,3] an oral dose of 130 mg of potassium iodide daily in adults (including pregnant and lactating women). Daily doses should be given until risk of exposure has passed and adjunctive measures have been implemented. Recommended daily doses of potassium iodide for children are:

- up to 1 month of age, 16 mg
- 1 month to 3 years, 32 mg
- 3 to 12 years (up to 18 years if body-weight is less than 70 kg), 65 mg

In the UK the oral dose recommended[4,5] is 100 mg of stable iodine (as 170 mg of potassium iodate) for adults (including pregnant women and women who are breast feeding) as soon as possible after exposure and before evacuation. Dosages for children are:

- 3 to 12 years, 50 mg of stable iodine (85 mg of potassium iodate)
- 1 month to 3 years, 25 mg of stable iodine (42.5 mg of potassium iodate)
- neonates, 12.5 mg of stable iodine (21.25 mg of potassium iodate) given as a single dose.

When evacuation is delayed, repeated daily doses may become necessary.

1. Halperin JA. Potassium iodide as a thyroid blocker— Three Mile Island today. *Drug Intell Clin Pharm* 1989; **23:** 422–7.
2. Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. *Am J Med* 1993; **94:** 524–32.
3. FDA Center for Drug Evaluation and Research. Guidance: potassium iodide as a thyroid blocking agent in radiation emergencies (issued December 2001). Available at: http://www.fda.gov/cder/guidance/4825fnl.htm (accessed 18/05/05)
4. DoH. Practical guidance on planning for incidents involving radioactivity: potassium iodate (stable iodine) prophylaxis in the event of a nuclear accident. PL/CMO(93)1 (issued 15 February 1993).
5. National Radiological Protection Board. Stable iodine prophylaxis: recommendations of the 2nd UK Working Group on Stable Iodine Prophylaxis. *Doc NRPB* 2001; **12** (3): 1–30. Also available at: http://www.hpa.org.uk/web/HPAwebfile/HPAweb_C/1194947336017 (accessed 01/08/08)

Preparations

BP 2008: Alcoholic Iodine Solution; Aqueous Iodine Oral Solution; Potassium Iodate Tablets; Sodium Iodide Injection;
BPC 1968: Compound Iodine Paint;
USP 31: Iodine Tincture; Iodine Topical Solution; Potassium Iodide Delayed-release Tablets; Potassium Iodide Oral Solution; Potassium Iodide Tablets; Strong Iodine Solution; Strong Iodine Tincture.

Proprietary Preparations (details are given in Part 3)
Austria: Jodid; Leukona-Jod-Bad†; ***Braz.:*** Elixir Americano†; Glitosslab; Iodeton; Iodetoss; Iodex; Iopotoss†; Minostoss†; Sifpol†; Xarope Neo; ***Canad.:*** Sclerodine; Thyro-Block†; ***Chile:*** Solucion De Lugol†; ***Cz.:*** Kalijev; ***Fin.:*** Jodix; ***Ger.:*** Jod beta; Jodetten; Jodgamma; Jodid; Leukona-Jod-Bad†; Mono-Jod; Strumex†; Thyprotect; Varigloban†; ***Hung.:*** Jod plus; Jodid; Jodomax; ***India:*** Collosol; ***Indon.:*** Yodsaben; ***Ital.:*** Chitodine; Goccemed; Sol-Jod†; ***Mex.:*** Yodolactina; ***Norw.:*** Jodosan; ***Philipp.:*** Jodid; Vitreolent; ***Pol.:*** Jodid; Jodox†; Vitreolent; ***Port.:*** Iodisis†; ***Rus.:*** Iodomarin (Йодомарин); Jodbalance (Йодбаланс); Jodid (Йодид); Microiodid (Микройодид); ***Spain:*** Yoduk; ***Thai.:*** Pose-Iodophore; ***Turk.:*** Tenturdiyot; ***UK:*** Bioiodine; ***USA:*** Geri-Dyne; Iodopen; Pima; SSKI; Thyro-Block; Thyro-Shield.

Multi-ingredient: ***Arg.:*** Antikatarata Plus; Iodotiazol†; Yodofrixon Salicilado†; ***Austral.:*** Asa Tones; Potassium Iodide and Stramonium Compound†; ***Austria:*** Jodthyrox; ***Belg.:*** Depuratif des Alpes; ***Braz.:*** ABC Solucao†; Antimicon†; Antiphlogistine†; Becantosse†; Bontoss†; Broncofisin†; Bronquidex; Brontoss; Dermicon; Dermol†; Dermycose†; Elixir 914†; Elixir de Marinheiro†; Endotussin; Expec; Expectobron†; Frenotossil†; Fungolab; Glycon; Glyteol Balsamico; Hebrin; Ikaflux; Iodepol†; Iodesin; Iodetal; Iodeto de Potassio Composto†; Iodeto de Potassio†; Iodeto de Potassium Composto†; Iodex com Salicilato de Metila; Iodopulmin†; Iol†; Iolin†; KI-Expectorante; Micotiazol; MM Expectorante; Pulmoforte†; Pulmonix†; Sedatux†; Spectolab; Teutoss†; Tossivitan†; Tussivit†; Tussol†; Xarope Iodo-Suma†; ***Canad.:*** Iode; ratio-Theo-Bronc; Vito Bronches†; ***Cz.:*** Aphlox†; Jodthyrox; Solutan†; ***Fr.:*** Folio; Nitrol; ***Ger.:*** Adelheid-Jodquelle, Tolzer; Eferox Jod; Jodthyrox; Krophan N†; L-Thyrox Jod; Thyreocomb N†; Thyronajod; ***Gr.:*** Iodocollyre; Tentil; Vitreolent; ***Hong Kong:*** Vitreolent; ***India:*** Cataresf; Cato-Bell; ***Israel:*** Iodax; ***Ital.:*** Antiadiposo; Esoform Jod 20 and 50; Facovit; Fertomcidina-U; Jodo Calcio Vitaminico; Linfoiodine; Polijodurato; Rubjovit; ***Malaysia:*** Vitreolent†; ***Mex.:*** Calciyodina; Iodarsolo B12†; Iodex Clasico; ***Pol.:*** Jodthyrox; ***Port.:*** Prelus†; ***Rus.:*** Jodthyrox (Йодтирокс); Neo-Anusol (Нео-анузол); Solutan (Солутан); Thyreocomb (Тиреокомб); ***Singapore:*** Vitreolent†; ***Spain:*** Adiod; Audione; Callicida Rojo; Depurativo Richelet; Encialina†; Nitroina; ***Switz.:*** Perpector†; Radix; Variglobin†; Vitreolent; ***Turk.:*** Neo Sedeks; ***UK:*** Nasciodine; TCP; ***USA:*** Elixophyllin-KI; Iodex with Methyl Salicylate; KIE; ORA5; Pediacof; Pedituss Cough; Phylorinol; Quadrinal; ***Venez.:*** Fedratal†; Iodex con Salicilato de Metilo; Na-Iodina Compuesta†; Yodalmina†.

Levothyroxine Sodium *(BANM, rINN)*

Levothyroxin sodná sůl hydrát; Lévothyroxine sodique; Levothyroxinnatrium; Levothyroxinum natricum; Levothyroxinum Natricum Hydricum; Levotiroksin Sodyum; Levotiroksino natrio druska; Levotiroxina sódica; Levotiroxin-nátrium; Levotyroksiininatrium; Levotyroxinnatrium; Lewotyroksyna sodowa; 3,5,3′,5′-Tetraiodo-L-thyronine Sodium; Thyroxine Sodium; L-Thyroxine Sodium; Thyroxinum Natricum; Tirossina; Tiroxina Sodica. Sodium 4-*O*-(4-hydroxy-3,5-di-iodophenyl)-3,5-di-iodo-L-tyrosine hydrate.

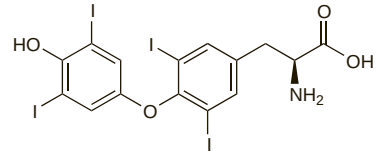
Левотироксин Натрий

$C_{15}H_{10}I_4NNaO_4.xH_2O$ = 798.9 (anhydrous).

CAS — 51-48-9 (levothyroxine); 55-03-8 (anhydrous levothyroxine sodium); 25416-65-3 (levothyroxine sodium, hydrate); 8065-29-0 (liotrix).

ATC — H03AA01.

ATC Vet — QH03AA01.



(levothyroxine)

NOTE. The abbreviation T_4 is often used for endogenous thyroxine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

Pharmacopoeias. In *Eur.* (see p.vii), *Int., Jpn, US*, and *Viet. Int.* includes the anhydrous form.

Ph. Eur. 6.2 (Levothyroxine Sodium). An almost white or slightly brownish-yellow powder or a fine, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Levothyroxine Sodium). The sodium salt of L-3,3′,5,5′-tetraiodothyronine. A light yellow to buff-coloured, odourless, hygroscopic, powder. It may assume a slight pink colour on exposure to light. Soluble 1 in 700 of water and 1 in 300 of alcohol; insoluble in acetone, in chloroform, and in ether; soluble in solutions of alkali hydroxides and in hot solutions of alkali carbonates. pH of a saturated solution in water is about 8.9. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

The adverse effects of levothyroxine are generally associated with excessive dosage and correspond to symptoms of hyperthyroidism. They may include tachycardia, palpitations, cardiac arrhythmias, increase in blood pressure, anginal pain, headache, restlessness, excitability, insomnia, tremors, muscle weakness and cramps, heat intolerance, sweating, flushing, fever, weight loss, menstrual irregularities, diarrhoea, and vomiting. These adverse reactions usually disappear after dosage reduction or temporary withdrawal of treatment. Thyroid storm has occasionally been reported after massive or chronic intoxication and convulsions, cardiac arrhythmias, heart failure, coma, and death have occurred.

In acute overdosage, activated charcoal may be used to reduce gastrointestinal absorption if ingestion of more than 10 mg by an adult, or 5 mg by a child, has occurred within 1 hour. Treatment is usually symptomatic and supportive; propranolol may be useful in controlling the symptoms of sympathetic overactivity. Levothyroxine overdosage requires an extended follow-up period as symptoms may be delayed for up to 6 days due to the gradual peripheral conversion of levothyroxine to tri-iodothyronine. US licensed product information has suggested that glucocorticoids may be given to inhibit this conversion.

Carcinogenicity. An association between the use of thyroid hormones and an increased risk of breast cancer in women has been proposed,[1] but a further analysis of the data did not confirm such an association,[2] and nor did later studies.[3-5]

1. Kapdi CC, Wolfe JN. Breast cancer. Relationship to thyroid supplements for hypothyroidism. *JAMA* 1976; **236:** 1124–7.
2. Mustacchi P, Greenspan F. Thyroid supplementation for hypothyroidism. An iatrogenic cause of breast cancer? *JAMA* 1977; **237:** 1446–7.
3. Wallace RB, *et al*. Thyroid hormone use in patients with breast cancer. Absence of an association. *JAMA* 1978; **239:** 958.
4. Shapiro S, *et al*. Use of thyroid supplements in relation to the risk of breast cancer. *JAMA* 1980; **244:** 1685–7.
5. Hoffman DA, *et al*. Breast cancer in hypothyroid women using thyroid supplements. *JAMA* 1984; **251:** 616–19.

Effects on the bones. Hyperthyroidism is a known risk factor for osteoporosis and theoretically thyroid hormone therapy may also be a risk factor. A review of over 3000 patients from 63 studies summarised the available evidence on the association of levothyroxine and bone mineral density.[1] It was stressed that current findings are complex and confusing and poor methodological quality makes comparison of results difficult. However, it was concluded that neither dose of levothyroxine nor duration of therapy had any relationship with bone mineral density: 31 studies showed no overall effect of levothyroxine, 23 studies provided partial negative and/or positive effects, while 9 showed overall negative effects. For postmenopausal women, particularly those with a history of hyperthyroidism, the review[1] recommended monitoring of thyroid hormone levels to avoid clinical hyperthyroidism, and screening for risk factors of osteoporosis; if warranted, bone densitometry, and appropriate management of any decline in bone mineral density, should be used.

1. Schneider R, Reiners C. The effect of levothyroxine therapy on bone mineral density: a systematic review of the literature. *Exp Clin Endocrinol Diabetes* 2003; **111:** 455–70.

Effects on the muscles. A woman with previous normal thyroid function developed periodic paralysis affecting the limbs after abusing levothyroxine, 100 micrograms twice daily for 2 weeks, in order to lose weight.[1] The attack subsided after treatment with intravenous potassium and withdrawal of the levothyroxine.

1. Chen YC, *et al*. Thyrotoxic periodic paralysis in a patient abusing thyroxine for weight reduction. *Ren Fail* 2001; **23:** 139–42.

Effects on the nervous system. Two children aged 8 and 11 years developed pseudotumor cerebri (benign intracranial hypertension) shortly after starting levothyroxine for hypothyroidism.[1] There have been further reports on individual children[2,3] and infants.[4]

Partial complex status epilepticus, with confusion, agitation, and continuous myoclonic jerks in the left side of the face and left hand, was seen in a hypothyroid patient with Turner's syndrome who was receiving levothyroxine for myxoedema coma.[5] The condition responded to anticonvulsants; the patient subsequently remained seizure-free on a reduced dose of levothyroxine and concomitant phenytoin.

1. Van Dop C, *et al*. Pseudotumor cerebri associated with initiation of levothyroxine therapy for juvenile hypothyroidism. *N Engl J Med* 1983; **308:** 1076–80.
2. McVie R. Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309:** 731.
3. Hymes LC, *et al*. Pseudotumor cerebri and thyroid-replacement therapy. *N Engl J Med* 1983; **309:** 732.
4. Raghavan S, *et al*. Pseudotumor cerebri in an infant after -thyroxine therapy for transient neonatal hypothyroidism. *J Pediatr* 1997; **130:** 478–80.
5. Duarte J, *et al*. Thyroxine-induced partial complex status epilepticus. *Ann Pharmacother* 1993; **27:** 1139.

Hypersensitivity. A hypersensitivity reaction (fever, eosinophilia, and liver dysfunction) was reported[1] in a 63-year-old hypothyroid woman with Hashimoto's thyroiditis during treatment with liothyronine or levothyroxine. Symptoms disappeared when the drugs were stopped. After an interval of 4 months liothyronine was gradually reintroduced without adverse effect.

Urticaria and angioedema have been described in a patient who received thyroid and levothyroxine.[2] In a further case similar re-

actions were attributed to the presence of sunset yellow as colouring agent in the proprietary levothyroxine preparation.[3]

1. Shibata H, *et al.* Hypersensitivity caused by synthetic thyroid hormones in a hypothyroid patient with Hashimoto's thyroiditis. *Arch Intern Med* 1986; **146:** 1624–5.
2. Pandya AG, *et al.* Chronic urticaria associated with exogenous thyroid use. *Arch Dermatol* 1990; **126:** 1238–9.
3. Lévesque H, *et al.* Reporting adverse drug reactions by proprietary name. *Lancet* 1991; **338:** 393.

Overdosage. In overdosage with thyroid drugs aggressive therapy is not normally justified in asymptomatic patients, although various regimens have been tried in large overdosage.

Massive overdoses of levothyroxine and liothyronine (up to 1000 times the normal dose over 2 to 12 days) have been described in small numbers of patients.[1-6] Symptoms of thyrotoxicosis can occur within the first 6 hours after ingestion of liothyronine but can be delayed for 2 to 5 days after levothyroxine, due to the time taken for metabolic conversion to liothyronine. Symptoms of thyrotoxicosis that have been reported include fever, arrhythmias, tachycardia, increased blood pressure, confusion, agitation, neurological complications, and coma.[1,2,5] Treatment of overdosage includes consideration of the use of activated charcoal and a beta blocker such as propranolol or metoprolol to treat tachyarrhythmia.[2,4,5] In most cases serious toxicity does not occur and patients recover with supportive therapy. Diuresis and haemodialysis do not enhance elimination because thyroid hormones are highly protein bound. It has also been concluded that plasmapheresis and haemoperfusion provide no significant clinical benefit.[4,6]

1. Kulig K, *et al.* Levothyroxine overdosage associated with seizures in a young child. *JAMA* 1985; **254:** 2109–10.
2. Binimelis J, *et al.* Massive thyroxine intoxication: evaluation of plasma extraction. *Intensive Care Med* 1987; **13:** 33–8.
3. Golightly LK, *et al.* Clinical effects of accidental levothyroxine ingestion in children. *Am J Dis Child* 1987; **141:** 1025–7.
4. Henderson A, *et al.* Lack of efficacy of plasmapheresis in a patient overdosed with thyroxine. *Anaesth Intensive Care* 1994; **22:** 463–4.
5. Hack JB, *et al.* Severe symptoms following a massive intentional L-thyroxine ingestion. *Vet Hum Toxicol* 1999; **41:** 323–6.
6. Solá E, *et al.* Massive triiodothyronine intoxication: efficacy of hemoperfusion? *Thyroid* 2002; **7:** 637–40.

Precautions

Levothyroxine is contra-indicated in untreated hyperthyroidism. It has a narrow therapeutic index and should be used with extreme caution in patients with cardiovascular disorders including angina, heart failure, myocardial infarction, and hypertension; lower initial doses, smaller increments, and longer intervals between increases should be used as necessary. An ECG performed before starting treatment with levothyroxine may help to distinguish underlying myocardial ischaemia from changes induced by hypothyroidism. Levothyroxine should also be introduced very gradually in elderly patients and those with long-standing hypothyroidism to avoid any sudden increase in metabolic demands. It should not be given to patients with adrenal insufficiency without adequate corticosteroid cover otherwise the thyroid replacement therapy might precipitate an acute adrenal crisis. Care is also required when levothyroxine is given to patients with diabetes mellitus or diabetes insipidus.

Tests of thyroid function are subject to alteration by a number of nonthyroidal clinical conditions and by a wide variety of drugs, some of which are mentioned under Interactions, below.

Abuse. For mention of abuse of levothyroxine by athletes for weight loss see Obesity, under Uses and Administration, below. For reference to periodic paralysis in a woman abusing levothyroxine as a slimming aid, see under Effects on the Muscles, above.

Adrenocortical insufficiency. Thyroid-hormone replacement without additional corticosteroids may precipitate acute adrenocortical insufficiency in patients with impaired adrenocortical function, including those with subclinical or unrecognised adrenocortical disease.[1] Prompt diagnosis and replacement of corticosteroids can prevent the development of a potentially fatal crisis. It has been pointed out that a raised concentration of thyroid-stimulating-hormone alone may not necessarily imply hypothyroidism in patients with chronic adrenocortical insufficiency.[2] Even confirmed hypothyroidism in these patients may not be permanent.

1. Fonseca V, *et al.* Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; **292:** 1185–6.
2. Davis J, Sheppard M. Acute adrenal crisis precipitated by thyroxine. *BMJ* 1986; **292:** 1595.

Anaemia. Four patients with iron deficiency anaemia and primary hypothyroidism developed palpitations and restlessness on treatment with levothyroxine sodium, and the drug had to be stopped. Upon correction of the anaemia with ferrous sulfate, all were able to tolerate levothyroxine therapy.[1] For a warning that ferrous sulfate reduces absorption of levothyroxine from the gastrointestinal tract, see Iron Salts under Interactions, below.

1. Shakir KMM, *et al.* Anemia: a cause of intolerance to thyroxine sodium. *Mayo Clin Proc* 2000; **75:** 189–92.

Breast feeding. Minimal amounts of thyroid hormones are distributed into breast milk.[1] Although levothyroxine in breast milk will be insufficient to treat any hypothyroidism in the suckling newborn, it has been suggested that it may mask detection of any hypothyroidism in such a neonate.[2] However, the *BNF* considers that the amounts involved are too small to affect tests for neonatal hypothyroidism. The American Academy of Pediatrics noted that no effects have been seen in breast-fed infants whose mothers were taking levothyroxine and as such considers its use to be usually compatible with breast feeding.[3]

1. Bennett PN, ed. *Drugs and human lactation.* Amsterdam: Elsevier, 1988.
2. Anonymous. Can a woman on thyroxine safely breast-feed her baby? *BMJ* 1977; **2:** 1589.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)

Cardiovascular disorders. There is a complex relationship between the heart and thyroid.[1] Cardiovascular abnormalities may be associated with hypothyroidism as well as with levothyroxine replacement therapy, hence the need for caution.

1. Gammage M, Franklyn J. Hypothyroidism, thyroxine treatment, and the heart. *Heart* 1997; **77:** 189–90.

Myasthenia. Thyroid hormones may occasionally precipitate or exacerbate a pre-existing myasthenic syndrome.[1,2]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; **24:** 304–21.
2. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Pregnancy. Most authorities consider that thyroid hormones do not readily cross the placenta. Placental transfer has been reported,[1] but in amounts so limited that a mother with physiological concentrations of thyroxine and tri-iodothyronine would not provide normal thyroid hormone concentrations to a fetus with congenital hypothyroidism.[2-4]

Levothyroxine requirements increase in hypothyroid women during early pregnancy. A small study involving 20 pregnancies found that the dose requirement rose from the sixth to the sixteenth week of gestation before reaching a plateau; a mean dose increase of nearly 50% was eventually required in 17 cases.[5] The authors recommended that all hypothyroid women should have their levothyroxine dose increased by 30% as soon as pregnancy was confirmed, to avoid any risk of an initial period of hypothyroxinaemia before the first obstetric visit. Thereafter, dosage should be adjusted according to serum-thyrotropin concentrations.

1. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989; **321:** 13–16.
2. Sack J, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1549–50.
3. Bachrach LK, Burrow GN. Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1549.
4. Vulsma T, *et al.* Maternal-fetal transfer of thyroxine. *N Engl J Med* 1989; **321:** 1550.
5. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; **351:** 241–9.

Interactions

Antiarrhythmics. *Amiodarone*[1] may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine with a rise in the concentration of inactive reverse tri-iodothyronine.

1. Hershman JM, *et al.* Thyroxine and triiodothyronine kinetics in cardiac patients taking amiodarone. *Acta Endocrinol (Copenh)* 1986; **111:** 193–9.

Antibacterials. Enzyme induction by *rifampicin*[1,2] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones.

Two patients with previously stable thyroid function while receiving levothyroxine were found to have developed hypothyroidism 3 to 4 weeks after starting oral treatment with *ciprofloxacin.*[3] In one patient increasing the dose of levothyroxine was ineffective and thyroid function only returned to normal after ciprofloxacin was withdrawn. In the other patient, giving the drugs 6 hours apart was sufficient to overcome the interaction.

1. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; **15:** 71–6.
2. Nolan SR, *et al.* Interaction between rifampin and levothyroxine. *South Med J* 1999; **92:** 529–31.
3. Cooper JG, *et al* Ciprofloxacin interacts with thyroid replacement therapy. *BMJ* 2005; **330:** 1002.

Anticoagulants. Thyroid hormones enhance the effects of *oral anticoagulants* (see under the interactions of Warfarin, p.1432). Patients on anticoagulant therapy therefore require careful monitoring when treatment with thyroid drugs is started or altered as the oral anticoagulant dose may need to be adjusted.

Antidepressants. Some drugs such as *lithium* act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism.[1]

The effects of levothyroxine in hypothyroid patients may be decreased by use with *sertraline*, and the dose of levothyroxine may need to be increased.[2]

For the effects of thyroid hormones on *tricyclic antidepressants* see under Amitriptyline, p.381.

1. Ramsay I. Drugs and non-thyroid induced changes in thyroid function tests. *Postgrad Med J* 1985; **61:** 375–7.
2. McCowen KC, *et al.* Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *N Engl J Med* 1997; **337:** 1010–11.

Antidiabetics. As thyroid status influences metabolic activity and most body systems, correction of hypothyroidism may affect other disease states and dosage of any drug treatment. In hypothyroid diabetics for instance, starting thyroid replacement therapy may increase their *insulin* or *oral hypoglycaemic* requirements.[1]

1. Refetoff S. Thyroid hormone therapy. *Med Clin North Am* 1975; **59:** 1147–62.

Antiepileptics. Enzyme induction by drugs such as *carbamazepine*,[1,2] *phenytoin*,[2,3] or *barbiturates*[4] enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones. Therefore, patients on thyroid replacement therapy may require an increase in their dose of thyroid hormone if these drugs are also given[5] and a decrease if the enzyme-inducing drug is withdrawn.[6] *Phenytoin*,[3] and *carbamazepine* may reduce protein binding by displacing the thyroid hormones from their plasma-binding sites. As thyroid hormones are highly protein bound, changes in binding might be expected to influence requirements in thyroid replacement therapy, but in practice there is little clinical evidence of any problems except with thyroid-function testing.

1. Connell JMC, *et al.* Changes in circulating thyroid hormones during short-term hepatic enzyme induction with carbamazepine. *Eur J Clin Pharmacol* 1984; **26:** 453–6.
2. Larkin JG, *et al.* Thyroid hormone concentrations in epileptic patients. *Eur J Clin Pharmacol* 1989; **36:** 213–6.
3. Franklyn JA, *et al.* Measurement of free thyroid hormones in patients on long-term phenytoin therapy. *Eur J Clin Pharmacol* 1984; **26:** 633–4.
4. Ohnhaus EE, Studer H. A link between liver microsomal enzyme activity and thyroid hormone metabolism in man. *Br J Clin Pharmacol* 1983; **15:** 71–6.
5. Blackshear JL, *et al.* Thyroxine replacement requirements in hypothyroid patients receiving phenytoin. *Ann Intern Med* 1983; **99:** 341–2.
6. Hoffbrand BI. Barbiturate/thyroid-hormone interaction. *Lancet* 1979; **ii:** 903–4.

Antimalarials. Increased thyroid-stimulating hormone concentration has been noted after the use of *chloroquine* with *proguanil* for malaria prophylaxis in a patient stabilised on levothyroxine.[1] Induction of liver enzymes by chloroquine resulting in increased metabolism of levothyroxine was suggested as the mechanism.

1. Munera Y, *et al.* Interaction of thyroxine sodium with antimalarial drugs. *BMJ* 1997; **314:** 1593.

Antineoplastics. Eight patients taking levothyroxine, subsequent to thyroidectomy, developed raised concentrations of thyroid-stimulating hormone (TSH) and clinical hypothyroidism when they were given *imatinib*. Increasing the levothyroxine dose reversed hypothyroidism in only 3 patients, but TSH concentrations returned to normal in all patients when imatinib was stopped. In contrast, these effects did not occur in 3 other patients with a normal functioning thyroid. The authors reasoned that imatinib might have stimulated the clearance of thyroxine and tri-iodothyronine by inducing uridine diphosphate glucuronosyltransferases, but evidence is needed to confirm this mechanism. They suggested that the dose of levothyroxine should be at least doubled, with close monitoring of thyroid function, before imatinib is given to patients with hypothyroidism.[1]

1. de Groot JWB, *et al.* Imatinib induces hypothyroidism in patients receiving levothyroxine. *Clin Pharmacol Ther* 2005; **78:** 433–8.

Antivirals. There have been reports of interactions between HIV protease inhibitors and levothyroxine. An increased dose of levothyroxine was necessary with *ritonavir*[1] whereas a decreased dose was needed with *indinavir*.[2]

1. Tseng A, Fletcher D. Interaction between ritonavir and levothyroxine. *AIDS* 1998; **12:** 2235–6.
2. Lanzafame M, *et al.* Interaction between levothyroxine and indinavir in a patient with HIV infection. *Infection* 2002; **30:** 54–5.

Beta blockers. Studies have indicated that plasma concentrations of *propranolol* are reduced in hyperthyroidism compared with the euthyroid state, probably due to increased clearance[1-4] and hypothyroid patients receiving chronic propranolol therapy have had a reduction in plasma-propranolol concentrations when given levothyroxine treatment.[2]

Propranolol may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine and a rise in the concentration of inactive reverse tri-iodothyronine.[5,6]

1. Feely J, *et al.* Increased clearance of propranolol in thyrotoxicosis. *Ann Intern Med* 1981; **94:** 472–4.
2. Feely J, *et al.* Plasma propranolol steady state concentrations in thyroid disorders. *Eur J Clin Pharmacol* 1981; **19:** 329–33.

3. Aro A, *et al.* Pharmacokinetics of propranolol and sotalol in hyperthyroidism. *Eur J Clin Pharmacol* 1982; **21:** 373–7.
4. Hallengren B, *et al.* Influence of hyperthyroidism on the kinetics of methimazole, propranolol, metoprolol, and atenolol. *Eur J Clin Pharmacol* 1982; **21:** 379–84.
5. Chambers JB, *et al.* The effects of propranolol on thyroxine metabolism and triiodothyronines production in man. *J Clin Pharmacol* 1982; **22:** 110–16.
6. Wilkins MR, *et al.* Effect of propranolol on thyroid homeostasis of healthy volunteers. *Postgrad Med J* 1985; **61:** 391–4.

Cardiac glycosides. Serum-digoxin concentrations appear to be lower in hyperthyroidism and higher in hypothyroidism,[1] which may contribute in part to the observed insensitivity of hyperthyroid patients to *digoxin* therapy,[2] although other mechanisms have been proposed.[3]

1. Croxson MS, Ibbertson HK. Serum digoxin in patients with thyroid disease. *BMJ* 1975; **3:** 566–8.
2. Huffman DH, *et al.* Digoxin in hyperthyroidism. *Clin Pharmacol Ther* 1977; **22:** 533–8.
3. Lawrence JR, *et al.* Digoxin kinetics in patients with thyroid dysfunction. *Clin Pharmacol Ther* 1977; **22:** 7–13.

Gastrointestinal drugs. *Sucralfate* reduces absorption of levothyroxine from the gastrointestinal tract[1,2] as does *aluminium hydroxide*,[3] and *calcium carbonate*.[4,5]

1. Sherman SI, *et al.* Sucralfate causes malabsorption of L-thyroxine. *Am J Med* 1994; **96:** 531–5.
2. Campbell JA, *et al.* Sucralfate and the absorption of -thyroxine. *Ann Intern Med* 1994; **121:** 152.
3. Liel Y, *et al.* Nonspecific intestinal adsorption of levothyroxine by aluminium hydroxide. *Am J Med* 1994; **97:** 363–5.
4. Schneyer CR. Calcium carbonate and reduction of levothyroxine efficacy. *JAMA* 1998; **279:** 750.
5. Singh N, *et al.* Effect of calcium carbonate on the absorption of levothyroxine. *JAMA* 2000; **283:** 2822–5.

General anaesthetics. Severe hypertension and tachycardia have been reported[1] when *ketamine* was used in patients taking levothyroxine.

1. Kaplan JA, Cooperman LH. Alarming reactions to ketamine in patients taking thyroid medication-treatment with propranolol. *Anesthesiology* 1971; **35:** 229–30.

Ion-exchange resins. *Colestyramine* significantly reduces the absorption of levothyroxine by binding with thyroid hormones in the gastrointestinal tract. The malabsorption of levothyroxine is minimised by allowing an interval of 4 to 5 hours to elapse between taking the two drugs.[1] A similar effect has been seen with *sodium polystyrene sulfonate*.[2]

1. Northcutt RC, *et al.* The influence of cholestyramine on thyroxine absorption. *JAMA* 1969; **208:** 1857–61.
2. McLean M, *et al.* Cation-exchange resin and inhibition of intestinal absorption of thyroxine. *Lancet* 1993; **341:** 1286.

Iron salts. *Ferrous sulfate* reduces absorption of levothyroxine from the gastrointestinal tract.[1]

1. Campbell NRC, *et al.* Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* 1992; **117:** 1010–13.

Lipid regulating drugs. Both decreased efficacy[1] and increased efficacy[2] of levothyroxine have been reported in individual patients given *lovastatin*. Increased thyroid stimulating hormone concentrations, requiring increased doses of levothyroxine, have been reported when *simvastatin* was begun.[3]

1. Demke DM. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; **321:** 1341–2.
2. Gormley GJ, Tobert JA. Drug interaction between thyroxine and lovastatin. *N Engl J Med* 1989; **321:** 1342.
3. Kisch E, Segall HS. Interaction between simvastatin and -thyroxine. *Ann Intern Med* 2005; **143:** 547.

NSAIDs. Falsely low concentrations of levothyroxine (T_4) or tri-iodothyronine (T_3) have been reported during treatment with some anti-inflammatory drugs. Serum TSH measurements are less affected by NSAIDs and therefore TSH would be the optimal screening test in patients receiving an NSAID.[1]

1. Samuels MH, *et al.* Variable effects of nonsteroidal antiinflammatory agents on thyroid test results. *J Clin Endocrinol Metab* 2003; **88:** 5710–16.

Sex hormones. *Oestrogen* therapy increases serum concentrations of thyroxine-binding globulin, thus increasing the amount of bound thyroxine. Normal thyroid function stimulates thyroxine synthesis to compensate for this effect and maintain normal free-thyroxine serum concentrations. In hypothyroidism, however, patients treated with exogenous levothyroxine who receive oestrogens, as in oral contraceptives or HRT,[1] may require an increase in levothyroxine dose. In contrast, *androgens* reduce the concentration of the binding globulin, which has resulted in clinical hyperthyroidism when given to postmenopausal women maintained on levothyroxine replacement therapy.[2]

Increased levothyroxine requirements were noted in a 79-year-old woman when she took *raloxifene* at the same time as her levothyroxine; absorption studies indicated that the effect could be reversed by separating doses of the two drugs by about 12 hours.[3]

1. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med* 2001; **344:** 1743–9.
2. Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. *Ann Intern Med* 1994; **121:** 247–51.
3. Siraj ES, *et al.* Raloxifene causing malabsorption of levothyroxine. *Arch Intern Med* 2003; **163:** 1367–70.

Sympathomimetics. Thyroid drugs increase metabolic demands and should therefore be used with caution with other drugs known to influence cardiac function, such as the *sympathomimetics*, as they may enhance this effect. In addition, thyroid hormones may increase receptor sensitivity to catecholamines.

Pharmacokinetics

Levothyroxine is variably absorbed from the gastrointestinal tract after oral doses. Fasting increases absorption. Once in the circulation, levothyroxine is extensively protein bound, principally to thyroxine-binding globulin (TBG) but also to a lesser extent to thyroxine-binding pre-albumin (TBPA) or to albumin. Levothyroxine has a plasma half-life of about 6 to 7 days in euthyroid subjects; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Levothyroxine is primarily metabolised in the liver and kidney to tri-iodothyronine (liothyronine) and, about 40%, to inactive reverse tri-iodothyronine (reverse T_3) both of which undergo further deiodination to inactive metabolites. Further metabolites result from the deamination and decarboxylation of levothyroxine to tetraiodothyroacetic acid.

Levothyroxine undergoes enterohepatic recycling and excretion in the faeces.

The distribution of thyroid hormones into breast milk and across the placenta is discussed under Breast Feeding and Pregnancy (above).

Uses and Administration

Levothyroxine is a thyroid hormone (see p.2165 for a description of the endogenous hormones) used as replacement therapy in the treatment of hypothyroidism (p.2167). It is given in conditions such as diffuse non-toxic goitre (see Goitre and Thyroid Nodules, p.2165) and Hashimoto's thyroiditis (see Hypothyroidism, p.2167) to suppress the secretion of thyroid-stimulating hormone (TSH) and hence prevent or reverse enlargement of the thyroid gland. Levothyroxine is also used to suppress TSH production in the treatment of thyroid carcinoma (p.674) and as a diagnostic agent for the differential diagnosis of hyperthyroidism. It is given with antithyroid drugs in the blocking-replacement regimen for the management of hyperthyroidism (p.2165).

The peak therapeutic effect of regular oral levothyroxine may not be achieved for several weeks and there is a slow response to changes in dosage. Similarly, effects may persist for several weeks after withdrawal. Levothyroxine is given as the sodium salt in a single daily dose. Its absorption can be irregular and it is probably best taken on an empty stomach, usually before breakfast.

The dose of levothyroxine sodium for the treatment of any thyroid disorder should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly.

In hypothyroidism an initial adult oral dose of 50 to 100 micrograms of levothyroxine sodium daily may be increased by 25 to 50 micrograms at intervals of about 4 weeks until the thyroid deficiency is corrected and a maintenance dose is established. The adult maintenance dose is usually between 100 and 200 micrograms daily. In elderly patients, in those with cardiovascular disorders, or in those with severe hypothyroidism of long standing, treatment should be introduced more gradually: an initial dose of 12.5 to 50 micrograms daily increased by increments of 12.5 to 25 micrograms at intervals of about 4 weeks may be appropriate.

In children, individualisation of dosage and monitoring of treatment is especially important. In the UK, the *BNFC* recommends the following oral doses:

- neonates: 10 to 15 micrograms/kg once daily initially, adjusted in steps of 5 micrograms/kg every 2 weeks or as needed, to a usual dose of 20 to 50 micrograms daily
- children aged 1 month to 2 years: 5 to 10 micrograms/kg once daily initially, adjusted in steps of 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual dose of 25 to 100 micrograms daily
- children aged 2 to 12 years: 5 micrograms/kg once daily initially, adjusted in steps of 25 micrograms daily every 2 to 4 weeks until metabolism is normalised, to a usual dose of 75 to 100 micrograms daily
- children aged 12 to 18 years: 50 to 100 micrograms once daily initially, adjusted in steps of 25 to 50 micrograms daily every 3 to 4 weeks until metabolism is normalised, to a usual dose of 100 to 200 micrograms daily

Doses are reduced by 50% in cardiac disease, and increased more slowly.

Levothyroxine sodium may be given by intravenous injection. It has also been given intramuscularly. In myxoedema (hypothyroid) coma doses of 200 to 500 micrograms by intravenous injection may be given initially. A further dose of 100 to 300 micrograms is given on the second day if no improvement is evident, and followed by daily supplements of about 100 to 200 micrograms until the patient is euthyroid and can tolerate oral doses.

Dextrothyroxine, the D-isomer of levothyroxine, has lipid regulating properties and has been used in the management of hypercholesterolaemia, but its use is severely limited by cardiotoxicity; it has only weak thyroid hormone activity.

◊ General references.

1. Mandel SJ, *et al.* Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med* 1993; **119:** 492–502.
2. Toft AD. Thyroxine therapy. *N Engl J Med* 1994; **331:** 174–80. Correction. *ibid.*; 1035.
3. Escobar-Morreale HF, *et al.* Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J Clin Endocrinol Metab* 2005; **90:** 4946–54.

Administration. There has been controversy over the bioequivalence or otherwise of different brands of levothyroxine. Most studies and reports have come from the USA and results may have depended to some extent on the particular brands compared. Formulations may also have changed which makes comparison of results difficult. One study[1] concluded that 2 generic levothyroxine products were bioequivalent and interchangeable with 2 branded products.

In 2004 the FDA issued guidance on the bioequivalence of several levothyroxine products on the US market but this was heavily criticised in a joint statement by several American professional societies.[2] In response these societies recommended to physicians that patients should be maintained on the same brand of levothyroxine and if the brand were changed then the patient's serum TSH should be retested and the dosage of levothyroxine re-titrated as necessary.

1. Dong BJ, *et al.* Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA* 1997; **277:** 1205–13.
2. American Association of Clinical Endocrinologists, The Endocrine Society, and American Thyroid Association. Joint position statement on the use and interchangeability of thyroxine products. Available at: http://www.aace.com/pub/pdf/guidelines/AACE-TES-ATA-ThyroxineProducts.pdf (accessed 20/06/06) See also American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists. Joint Statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. *Thyroid* 2004; **14:** 486.

Cardiomyopathies. Management of dilated cardiomyopathy (p.1163) usually involves conventional therapy for heart failure, but a small study has reported benefit from short-term use of levothyroxine.[1] Levothyroxine was well tolerated but thyroid-stimulating hormone levels were reduced, which might limit long-term therapy.

1. Moruzzi P, *et al.* Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. *Am J Med* 1996; **101:** 461–7.

Depression. While thyroid hormones may increase the activity of tricyclic antidepressants (see Thyroid Hormones, under Interactions of Amitriptyline, p.381), the benefits in the augmentation treatment of depression (p.373) are debatable. A meta-analysis[1] of 8 studies involving 292 patients with refractory depression treated with liothyronine in addition to tricyclic antidepressants indicated that such therapy was effective in a subgroup of cases but that the small number of patients studied made additional placebo-controlled data desirable.

In non-refractory depression a meta-analysis[2] also indicated a benefit when liothyronine was added to tricyclic antidepressants although it was acknowledged that many of the studies were old

with methodological limitations. However, a controlled trial of liothyronine with paroxetine could not confirm any advantage of additive therapy.[3]

1. Aronson R, *et al.* Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Arch Gen Psychiatry* 1996; **53:** 842–8.
2. Altshuler LL, *et al.* Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* 2001; **158:** 1617–22.
3. Appelhof BC, *et al.* Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab* 2004; **89:** 6271–6.

Obesity. Thyroid drugs have been tried in the treatment of obesity (p.2149) in euthyroid patients, but they produce only temporary weight loss, mainly of lean body-mass, and can produce serious adverse effects, especially cardiac complications.[1] Hypothyroidism has also been reported[2] when these drugs were withdrawn from previously euthyroid patients being treated for simple obesity. Levothyroxine appears to have been abused by some athletes to promote weight loss.[3]

1. Rivlin RS. Therapy of obesity with hormones. *N Engl J Med* 1975; **292:** 26–9.
2. Dornhorst A, *et al.* Possible iatrogenic hypothyroidism. *Lancet* 1981; **i:** 52.
3. MacAuley D. Drugs in sport. *BMJ* 1996; **313:** 211–15.

Urticaria. There is some suggestion that chronic urticaria (p.1584) may be associated with thyroid autoimmunity and that treatment with thyroid hormones may result in clinical remission.[1] In one study, a nine-year-old boy was successfully treated for chronic urticaria with levothyroxine therapy at doses of 50 to 100 micrograms daily.[2] The authors advised screening for thyroid function and anti-thyroid microsomal antibodies in cases of chronic urticaria as these patients may benefit from thyroid hormone therapy. A small investigative study concluded that treatment with levothyroxine sodium (in hypothyroid patients) or antithyroid drugs (in patients with Graves' disease) is of benefit in patients with severe chronic urticaria associated with thyroid autoimmunity.[3]

1. Rumbyrt JS, *et al.* Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; **96:** 901–5.
2. Dreyfus DH, *et al.* Steroid-resistant chronic urticaria associated with anti-thyroid microsomal antibodies in a nine-year-old boy. *J Pediatr* 1996; **128:** 576–8.
3. Gaig P, *et al.* Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity *J Investig Allergol Clin Immunol* 2000; **10:** 342–5.

Preparations

BP 2008: Levothyroxine Tablets;
USP 31: Levothyroxine Sodium Tablets; Liotrix Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Euthyrox; Juno†; T4; ***Austral.:*** Eutroxsig; Oroxine; ***Austria:*** Euthyrox; Neothyron; Thyrex; ***Belg.:*** Elthyrone; Euthyrox; Thyrax; ***Braz.:*** Euthyrox; Puran T4; Synthroid; Tetroid; Tiroidin; ***Canad.:*** Eltroxin; Euthyrox; Synthroid; ***Chile:*** Esaldox; Eutirox; ***Cz.:*** Eltroxin; Euthyrox; Letrox; Thyrax†; ***Denm.:*** Eltroxin; ***Fr.:*** Levothyrox; ***Ger.:*** Berlthyrox; Eferox; Euthyrox; L-Thyrox; Lixin; Thevier; ***Gr.:*** Levothroid; T-4; Thyro-4; Thyrohormone; ***Hong Kong:*** Eltroxin; ***Hung.:*** Euthyrox; Letrox; ***India:*** Eltroxin; ***Indon.:*** Euthyrox; Thyrax; ***Irl.:*** Eltroxin; ***Israel:*** Eltroxin; ***Ital.:*** Eutirox; Tiracrin; Tirosint; ***Jpn:*** Thyradin-S; ***Malaysia:*** Oroxine; ***Mex.:*** Abutiroi; Cynocuatro; Daltroid†; Eutirox; Sintrocid†; Tiroidine; ***Neth.:*** Eltroxin; Euthyrox; Thyrax; ***Norw.:*** Levaxin; ***NZ:*** Eltroxin; ***Philipp.:*** Eltroxin; Euthyrox; Thyrax; Thyrohex; ***Pol.:*** Eferox; Eltroxin; Euthyrox; Letrox; ***Port.:*** Eutirox; Letequatro; Letter; Thyrax; ***Rus.:*** Bagothyrox (Баготирокс); Euthyrox (Эутирокс); ***S.Afr.:*** Eltroxin; ***Singapore:*** Eltroxin; Euthyrox; Oroxine; ***Spain:*** Dexnon; Eutirox; Levothroid; ***Swed.:*** Euthyrox; Levaxin; ***Switz.:*** Eltroxine; Euthyrox; ***Thai.:*** Elthyro; Eltroxin; Euthyrox; Pondtroxin; Thyrosit; ***Turk.:*** Levotiron; Tefor; ***UK:*** Eltroxin; Evotrox; ***USA:*** Levothroid; Levoxyl; Novothyrox; Synthroid; Unithroid; ***Venez.:*** Euthyrox; Thyrax.

Multi-ingredient: ***Arg.:*** Eutroid; Levotrin; ***Austria:*** Combithyrex; Jodthyrox; Novothyral; Prothyrid; ***Belg.:*** Novothyral; ***Braz.:*** Tyroplus†; ***Chile:*** Novothyral; ***Cz.:*** Jodthyrox; Novothyral†; Thyreotom; ***Fr.:*** Euthyral; ***Ger.:*** Eferox Jod; Jodthyrox; L-Thyrox Jod; Novothyral; Prothyrid; Thyreocomb N†; Thyreotom†; Thyronajod; ***Gr.:*** Dithyron; ***Ital.:*** Dermocinetic; Somatoline; Tiroide Amsa; ***Mex.:*** Cynoplus; Novotiral; Proloid S†; ***Pol.:*** Jodthyrox; Novothyral; ***Rus.:*** Jodthyrox (Йодтирокс); Novothyral (Новотирал); Thyreocomb (Тиреокомб); Thyreotom (Тиреотом); ***S.Afr.:*** Diotroxin; ***Switz.:*** Novothyral; ***Turk.:*** Bitiron; ***USA:*** Thyrolar.

Liothyronine Sodium *(BANM, rINNM)*

Liothyronin sodná sůl; Liothyronine sodique; Liothyroninum natricum; Liotironin Sodyum; Liotironina sódica; Liotironin-nátrium; Liotironino natrio druska; Liotyroniininatrium; Liotyronina sodowa; Liotyroninnatrium; Natrii Liothyroninum; Sodium Liothyronine; L-Tri-iodothyronine Sodium; 3,5,3′-Tri-iodo-L-thyronine Sodium; Tri-iodotironin Sodyum. Sodium 4-*O*-(4-hydroxy-3-iodophenyl)-3,5-di-iodo-L-tyrosine.

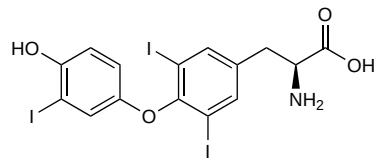
Натрий Лиотиронин

$C_{15}H_{11}I_3NNaO_4$ = 673.0.

CAS — 6893-02-3 (liothyronine); 55-06-1 (liothyronine sodium); 8065-29-0 (liotrix).

ATC — H03AA02.

ATC Vet — QH03AA02.



(liothyronine)

NOTE. The abbreviation T_3 is often used for endogenous tri-iodothyronine in medical and biochemical reports. Liotrix is *USAN* for a mixture of liothyronine sodium with levothyroxine sodium.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Liothyronine Sodium). A white or almost white or slightly coloured powder. Practically insoluble in water; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store at 2° to 8° in airtight containers. Protect from light.

USP 31 (Liothyronine Sodium). A light tan, odourless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in most other organic solvents. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Levothyroxine Sodium, p.2171.

Interactions

As for Levothyroxine Sodium, p.2172.

Pharmacokinetics

Liothyronine is readily and almost completely absorbed from the gastrointestinal tract. Once in the circulation, liothyronine binds principally to thyroxine-binding globulin (TBG), although less strongly than levothyroxine; some is also bound to thyroxine-binding pre-albumin (TBPA) or to albumin. Liothyronine has a plasma half-life in euthyroidism of about 1 to 2 days; the half-life is prolonged in hypothyroidism and reduced in hyperthyroidism.

Liothyronine is metabolised by deiodination to inactive di-iodothyronine and mono-iodothyronine. Iodine released by deiodination is largely reused within the thyroid cells. Further metabolites result from deamination and decarboxylation to tiratricol (triac).

Uses and Administration

Liothyronine is a thyroid hormone (see p.2165). It is used in the treatment of hypothyroidism (p.2167), and is believed to be more active than levothyroxine (p.2173). The onset of action of liothyronine is rapid, developing within a few hours, and therefore it tends to be used in circumstances where this, and its short duration of action, are useful, particularly in hypothyroid (myxoedema) coma.

With regular dosing the peak therapeutic effect is usually achieved after 3 days; on withdrawal its effects may persist for 1 to 3 days.

The dose of liothyronine should be individualised on the basis of clinical response and biochemical tests and should be monitored regularly. Although liothyronine is given as the sodium salt, doses can be expressed in terms of liothyronine sodium or liothyronine; the doses below are in terms of liothyronine sodium. Liothyronine sodium 10.3 micrograms is equivalent to about 10 micrograms of liothyronine. Liothyronine sodium 20 to 25 micrograms is generally considered to be equivalent in activity to about 100 micrograms of levothyroxine sodium.

In **hypothyroidism** a usual initial adult oral dose is 5 to 25 micrograms daily, increased gradually to a maintenance dose of 60 to 75 micrograms daily in 2 to 3 divided doses, although up to 100 micrograms daily may be required in some patients. In elderly patients, in those with cardiovascular disorders, or in those with severe long-standing hypothyroidism, treatment should be introduced with doses at the low end of the range, with smaller increments, and longer intervals between increases, as necessary.

In **myxoedema coma** liothyronine sodium may be given intravenously in a dose of 5 to 20 micrograms by slow intravenous injection, repeated as necessary, usually at intervals of 12 hours; the minimum interval between doses is 4 hours. An alternative regimen advocates an initial dose of 50 micrograms intravenously followed by further injections of 25 micrograms every 8 hours until improvement occurs; the dosage may then be reduced to 25 micrograms intravenously twice daily.

Liothyronine has also been given in the **diagnosis** of hyperthyroidism in adults. Failure to suppress the uptake of radio-iodine after several days of receiving liothyronine sodium suggests a diagnosis of hyperthyroidism.

Liothyronine hydrochloride has also been used.

Preparations

BP 2008: Liothyronine Tablets;
USP 31: Liothyronine Sodium Tablets; Liotrix Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Tertroxin; ***Braz.:*** Cynomel†; ***Canad.:*** Cytomel; ***Cz.:*** Tertroxin†; ***Fr.:*** Cynomel; ***Ger.:*** Thybon; Thyrotardin N; ***Gr.:*** Cynomel†; T-3; ***Ital.:*** Dispon†; Ti-Tre; ***Mex.:*** Cynomel; Liotrex; Triyotex; ***Neth.:*** Cytomel; ***NZ:*** Tertroxin; ***Port.:*** Neo-Tiroimade; ***S.Afr.:*** Tertroxin; ***Thai.:*** Tertroxin†; ***Turk.:*** Tiromel; ***UK:*** Tertroxin†; Triiodothyronine Injection; ***USA:*** Cytomel; Triostat; ***Venez.:*** Tertroxin†.

Multi-ingredient: ***Arg.:*** Eutroid; Levotrin; Tresite F; ***Austria:*** Combithyrex; Novothyral; Prothyrid; ***Belg.:*** Novothyral; ***Braz.:*** Tyroplus†; ***Chile:*** Novothyral; ***Cz.:*** Novothyral†; Thyreotom; ***Fr.:*** Euthyral; ***Ger.:*** NeyNormin N (Revitorgan-Dilutionen N Nr 65)†; NeyTumorin N (Revitorgan-Dilutionen N Nr 66)†; Novothyral; Prothyrid; Thyreotom†; ***Gr.:*** Dithyron; ***Ital.:*** Tiroide Amsa; ***Mex.:*** Cynoplus; Novotiral; Proloid S†; Redotex; ***Pol.:*** Novothyral; ***Rus.:*** Novothyral (Новотирал); Thyreocomb (Тиреоком6); Thyreotom (Тиреотом); ***S.Afr.:*** Diotroxin; ***Switz.:*** Novothyral; ***Turk.:*** Bitiron; ***USA:*** Thyrolar.

Potassium Perchlorate

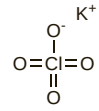
Chloristan draselný; Kalii perchloras; Kalio perchloratas; Kaliumperkloraatti; Kaliumperklorat; Kálium-perklorát; Perclorato potásico; Potassium, perchlorate de.

$KClO_4$ = 138.5.

CAS — 7778-74-7.

ATC — H03BC01.

ATC Vet — QH03BC01.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Potassium Perchlorate). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; practically insoluble in alcohol.

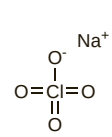
USP 31 (Potassium Perchlorate). pH of a 0.1M solution in water is between 5.0 and 6.5.

Sodium Perchlorate

Perclorato sódico; Sodu nadchloran.

$NaClO_4$ = 122.4.

CAS — 7601-89-0 (anhydrous sodium perchlorate); 7791-07-3 (sodium perchlorate monohydrate).



(anhydrous sodium perchlorate)

Handling. Potassium and sodium perchlorate have been used for the illicit preparation of explosives or fireworks; care is required with their supply. Great caution should be taken in handling perchlorates in solution or in the dry state as explosions may occur if brought into contact with organic or other readily oxidisable substances.

Adverse Effects

Fever and rashes have occurred after use of perchlorate. Some patients may experience nausea and vomiting. Potassium perchlorate seldom produces adverse effects when given as a single dose for diagnostic purposes. Prolonged use as an antithyroid drug has been