liver, and excreted in the urine. Less than 12% of a dose of thiamazole may be excreted as unchanged drug. 3-Methyl-2-thiohydantoin has been identified as a metabolite of thiamazole. The elimination half-life may be increased in hepatic and renal impairment.

Thiamazole crosses the placenta and is distributed into breast milk.

◊ References to the pharmacokinetics of carbimazole and thiamazole.

1. Skellern GG, *et al.* The pharmacokinetics of methimazole after oral administration of carbimazole and methimazole, in hyperthyroid patients. *Br J Clin Pharmacol* 1980; **9:** 137–43.
2. Kampmann JP, Hansen JM. Clinical pharmacokinetics of antithyroid drugs. *Clin Pharmacokinet* 1981; **6:** 401–28.
3. Jansson R, *et al.* Intrathyroidal concentrations of methimazole in patients with Graves' disease. *J Clin Endocrinol Metab* 1983; **57:** 129–32.
4. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
5. Jansson R, *et al.* Pharmacokinetic properties and bioavailability of methimazole. *Clin Pharmacokinet* 1985; **10:** 443–50.

Uses and Administration

Carbimazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p.2165). It is used in the management of hyperthyroidism (p.2165), including the treatment of Graves' disease, the preparation of hyperthyroid patients for thyroidectomy, as an adjunct to radio-iodine therapy, and in the treatment of thyroid storm.

Carbimazole is completely metabolised to thiamazole and it is this metabolite that is responsible for the antithyroid activity of carbimazole.

Carbimazole is given orally in a typical initial dosage of 15 to 40 mg daily, in divided doses; occasionally up to 60 mg daily may be required. Control of symptoms is usually achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to the smallest amount that will maintain the euthyroid state. Typical maintenance doses are 5 to 15 mg daily, which may be given as a single daily dose.

Treatment in children should be undertaken by a specialist. The *BNFC* recommends an initial dose of 250 micrograms/kg three times daily for neonates and children up to 12 years of age. Children aged 12 to 18 years may be given 10 mg three times daily initially. Doses are adjusted according to response; higher initial doses may be needed in thyrotoxic crisis.

Carbimazole is also given orally in a dose of 20 to 60 mg daily, with supplemental levothyroxine, as a *blocking-replacement regimen*.

Either form of maintenance treatment is usually continued for at least a year, and often for 18 months; up to 2 years of treatment may be required.

Preparations

BP 2008: Carbimazole Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Neo-Mercazole; ***Austria:*** Carbistad; ***Denm.:*** Neo-Mercazole; ***Fin.:*** Tyrazol; ***Fr.:*** Neo-Mercazole; ***Ger.:*** Car; Neo-Thyreostat†; ***Gr.:*** Thyrostat; ***Hong Kong:*** Cazole; ***India:*** Neo-Mercazole; ***Indon.:*** Neo-Mercazole; ***Irl.:*** Neo-Mercazole; ***Malaysia:*** Camazol†; ***Norw.:*** Neo-Mercazole; ***NZ:*** Neo-Mercazole; ***Philipp.:*** Neo-Mercazole; ***S.Afr.:*** Neo-Mercazole; ***Singapore:*** Camazol; Cazole†; ***Spain:*** Neo Tomizol; ***Switz.:*** Neo-Mercazole; ***UK:*** Neo-Mercazole.

Dibromotyrosine

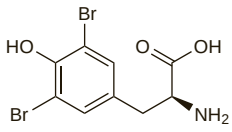
Dibromotirosina. 3,5-Dibromo-L-tyrosine.

$C_9H_9Br_2NO_3$ = 339.0.

CAS — 300-38-9.

ATC — H03BX02.

ATC Vet — QH03BX02.



Profile

Dibromotyrosine is an antithyroid drug used in the treatment of hyperthyroidism (p.2165) in doses of 300 to 900 mg daily by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Bromotiren.

Multi-ingredient: ***Ital.:*** Bromazolo.

Iodine

Iod; Iode; Iodium; Iodo; Iodum; Iyot; Jód; Jod; Jodas; Jodi; Jodum; Yodo.

I_2 = 253.80894.

CAS — 7553-56-2.

ATC — D08AG03.

ATC Vet — QD08AG03.

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

Ph. Eur. 6.2 (Iodine). Greyish-violet, brittle plates or fine crystals, with a metallic sheen. It is slowly volatile at room temperature. Very slightly soluble in water; soluble in alcohol; slightly soluble in glycerol; very soluble in concentrated solutions of iodides.

USP 31 (Iodine). Heavy, greyish-black plates or granules with a metallic sheen and a characteristic odour. Soluble 1 in 3000 of water, 1 in 13 of alcohol, 1 in 4 of carbon disulfide, and 1 in 80 of glycerol; freely soluble in chloroform, in ether, and in carbon tetrachloride; soluble in solutions of iodides. Store in airtight containers.

Incompatibility. With acetone, iodine forms a pungent irritating compound.

Potassium Iodate

Iodato potásico; Potasu jodan.

KIO_3 = 214.0.

CAS — 7758-05-6.

Pharmacopoeias. In *Br.*, *Chin.*, and *It.*

BP 2008 (Potassium Iodate). A white crystalline powder with a slight odour. Slowly soluble in water; insoluble in alcohol. A 5% solution in water has a pH of 5.0 to 8.0.

Potassium Iodide

Iodeto de Potássio; Ioduro potásico; Jodid draselný; Kalii Iodetum; Kalii iodidum; Kalii Jodidum; Kalio jodidas; Kalium Iodatum; Kalium Jodatum; Kaliumjodid; Kálium-jodid; Kaliumjodidi; Pot. Iod.; Potassii Iodidum; Potassium (Iodure de); Potassium, iodure de; Potasu jodek; Potasyum Iyodür.

KI = 166.0.

CAS — 7681-11-0.

ATC — R05CA02; S01XA04; V03AB21.

ATC Vet — QR05CA02; QS01XA04; QV03AB21.

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

Ph. Eur. 6.2 (Potassium Iodide). A white or almost white powder or colourless crystals. Very soluble in water; soluble in alcohol; freely soluble in glycerol. Protect from light.

USP 31 (Potassium Iodide). Hexahedral crystals, either transparent and colourless or somewhat opaque and white, or a white, granular powder. It is slightly hygroscopic. Soluble 1 in 0.7 of water and 1 in 0.5 of boiling water, 1 in 22 of alcohol, and 1 in 2 of glycerol. Its solutions are neutral or alkaline to litmus.

Sodium Iodide

Iodeto de Sódio; Ioduro sódico; Jodid sodný; Natrii Iodetum; Natrii iodidum; Natrii Jodidum; Natrio jodidas; Natrium Iodatum; Natriumjodid; Nátrium-jodid; Natriumjodidi; Sod. Iod.; Sodii Iodidum; Sodium (Iodure de); Sodium, iodure de; Sodu jodek; Sodyum Iyodür.

NaI = 149.9.

CAS — 7681-82-5.

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

Ph. Eur. 6.2 (Sodium Iodide). Colourless crystals or white or almost white, crystalline powder. It is hygroscopic. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Sodium Iodide). Colourless, odourless crystals, or white crystalline powder. It is deliquescent in moist air and develops a brown tint upon decomposition. Soluble 1 in 0.6 of water, 1 in 2 of alcohol, and 1 in 1 of glycerol. Store in airtight containers.

Adverse Effects and Treatment

Iodine and iodides, whether applied topically or given systemically, can give rise to hypersensitivity reactions which may include urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia.

Inhalation of iodine vapour is very irritating to mucous membranes.

Iodine and iodides have variable effects on the thyroid (see below) and can produce goitre and hypothyroidism as well as hyperthyroidism (the Iod-Basedow or Jod-Basedow phenomenon). Goitre and hypothyroidism have also occurred in infants born to mothers who had taken iodides during pregnancy.

Prolonged use may lead to a range of adverse effects, often called 'iodism', some of which may again be due to hypersensitivity. Adverse effects include metallic taste, increased salivation, burning or painful mouth; there may be acute rhinitis, coryza-like symptoms, and swelling and inflammation of the throat. Eyes may be irritated and swollen and there may be increased lachrymation. Pulmonary oedema, dyspnoea, and bronchitis may develop. Skin reactions include acneform or, more rarely, severe eruptions (iododerma). Other reported effects include depression, insomnia, impotence, headache, and gastrointestinal disturbances, notably nausea, vomiting, and diarrhoea.

The symptoms of acute poisoning from ingestion of iodine are mainly due to its corrosive effects on the gastrointestinal tract; a disagreeable metallic taste, vomiting, abdominal pain, and bloody diarrhoea occur. Thirst and headache have been reported. Systemic toxicity may lead to shock, tachycardia, hypotension, fever, metabolic acidosis and renal impairment. Death may be due to circulatory failure, oedema of the epiglottis resulting in asphyxia, aspiration pneumonia, or pulmonary oedema. Oesophageal stricture may occur if the patient survives the acute stage.

Victims of acute poisoning have been given copious draughts of milk or starch mucilage; lavage should probably not be attempted, and certainly not unless the ingested iodine was in sufficiently dilute form not to produce gastrointestinal corrosion. Other possible oral treatments include activated charcoal or sodium thiosulfate solution (usually as a 1% solution) to reduce iodine to the less toxic iodides.

Effects on the thyroid. Iodide may be isolated by the body from a variety of sources, including an iodine-rich diet, or some disinfectants and drugs containing iodine (see also under Amiodarone, p.1212). Although iodine is required for the production of thyroid hormones, excessive quantities can cause hyperthyroidism, or even paradoxical goitre and hypothyroidism.

The normal daily requirement ranges from 100 to 300 micrograms.[1,2] Quantities of 500 micrograms to 1 mg daily probably have no untoward effects on thyroid function in most cases.[2] When progressively larger doses are given there is an initial rise in thyroid hormone production, but at still higher doses, production decreases (the Wolff-Chaikoff effect). This effect is usually seen with doses of more than about 2 mg daily, but is normally transient, adaptation occurring on repeated dosage. In certain individuals a lack of adaptation produces a chronic inhibition of thyroid hormone synthesis leading to goitre and **hypothyroidism**.[1,2]

Excess iodine may also induce **hyperthyroidism** (the Iod-Basedow or Jod-Basedow phenomenon). Iodine-induced hyperthyroidism has been associated with iodine prophylaxis programmes in developing countries.[3] The highest incidence of hyperthyroidism has been reported to occur 1 to 3 years after supplementation begins, with the incidence returning to normal within 3 to 10 years despite continued iodine exposure.[4] Elderly subjects and those with nodular goitres have been found to be at greatest risk.

To overcome any adverse effects on thyroid function as a result of iodine prophylaxis during **pregnancy**, WHO has issued guidelines on the safe use of iodised oil during gestation.[5,6] There is some evidence that the use of iodine-containing antiseptics on pregnant women and neonates may cause disturbances in thyroid function.[7,8]

1. Arthur JR, Beckett GJ. Thyroid function. *Br Med Bull* 1999; **55:** 658–68.
2. WHO. Iodine. In *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 49–71.
3. Delange F, *et al.* Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid* 1999; **9:** 545–56.
4. Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. *Medicine (Baltimore)* 1983; **62:** 1–20.
5. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; **74:** 1–3.
6. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; **74:** 101–8.
7. Linder N *et al.* Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; **131:** 434–9.
8. Weber G *et al.* Neonatal transient hypothyroidism: aetiological study. *Arch Dis Child Fetal Neonatal Ed* 1998; **79:** F70–2.

Precautions

Caution is necessary if preparations containing iodine or iodides are taken for long periods, and such preparations should not be taken regularly during pregnancy except when iodine supplementation is required. Caution is also required when giving iodine or iodides to children. Patients over the age of 45 years or with nodular goitres are especially susceptible to hyperthyroidism when given iodine supplementation. Reduced doses should therefore be used and supplementation with iodised oil may not be appropriate.

Solutions of iodine applied to the skin should not be covered with occlusive dressings. The disinfectant activity of iodine is reduced by alkalis as well as by protein.

As iodine and iodides can affect the thyroid gland, their use may interfere with tests of thyroid function.

Breast feeding. Iodine is concentrated by the mammary gland into breast milk to ensure an adequate supply to the breast-fed infant. Since this is dependent on the maternal dietary intake,[1] WHO recommends a daily iodine intake of 200 micrograms for lactating women, see Iodine Deficiency Disorders, below.

The *BNFC* considers treatment with iodine or iodides to be a contra-indication to breast feeding. However, the American Academy of Pediatrics[2] considers that such treatment is usually compatible with breast feeding although it is noted that goitre or effects on thyroid function have been reported. Any risk is not confined to oral treatment: transient neonatal hypothyroidism has been reported in a breast-fed infant whose mother was treated with iodine tampons,[3] and for a report of increased milk-iodine concentrations associated with vaginal povidone-iodine see p.1659.

1. Semba RD, Delange F. Iodine in human milk: perspectives for infant health. *Nutr Rev* 2001; **59:** 269–78.
2. 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)
3. Casteels K, *et al.* Transient neonatal hypothyroidism during breastfeeding after post-natal maternal topical iodine treatment. *Eur J Pediatr* 2000; **159:** 716–17.

Interactions

The effects of iodine and iodides on the thyroid may be altered by other compounds including amiodarone and lithium.

Pharmacokinetics

Iodine is slightly absorbed when applied to the skin. When taken by mouth, iodine preparations (which are converted to iodide) and iodides are transported to, and concentrated in, the thyroid gland (see p.2165). Iodides not taken up by the thyroid are excreted mainly in the urine, with smaller amounts appearing in the faeces, saliva, and sweat. They cross the placenta and are distributed into breast milk.

Uses and Administration

Iodine is an essential trace element in the human diet, necessary for the formation of thyroid hormones (see p.2165), and consequently it is used in iodine deficiency and thyroid disorders. It also has antimicrobial activity.

For the prophylaxis and treatment of **iodine deficiency disorders** (below) it may be given as potassium or sodium iodide, iodised oil, or potassium iodate. Each g of potassium iodide represents about 6 mmol of potassium and of iodine. Each g of sodium iodide represents about 6.7 mmol of sodium and of iodine. Each g of potassium iodate represents about 4.7 mmol of potassium and of iodine.

In the pre-operative management of **hyperthyroidism** (p.2165) iodine and iodides are used with antithyroid drugs such as carbimazole, thiamazole, or propylthiouracil. Such use has been thought to render the thyroid firm and avoid the increased vascularity and friability (with increased risk of haemorrhage) that may result from the use of an antithyroid drug alone. However, there is little evidence of a beneficial effect.

Iodine may be given as a solution with potassium iodide (Aqueous Iodine Oral Solution BP 2008; Lugol's Solution or Strong Iodine Solution USP 31) which contains in each mL 130 mg of free and combined iodine; a dose of 0.1 to 0.3 mL in milk or water is given three times daily for 10 to 14 days. Alternatively, potassium iodide has been given in doses of up to 250 mg three times daily with food. Solutions of potassium iodide intended for oral use should be given well diluted to avoid gastric irritation. Potassium iodide may also be given 1 hour after an antithyroid drug as part of the management of thyroid storm; doses as high as 500 mg every 4 hours have been suggested. Sodium iodide has been given by intravenous injection as part of the management of thyroid storm.

Radioactive sodium iodide (see Iodine-131, p.2054) is also used for the treatment of hyperthyroidism, especially when medical treatment or compliance is problematic, in patients with cardiac disease, or in patients who relapse after thyroidectomy.

Potassium iodide has been tried in the treatment of benign **thyroid nodules** (p.2165).

Potassium iodide or potassium iodate are taken by mouth for **radiation protection** (below) to saturate the thyroid when uptake of radio-iodine by the gland is not desired.

Iodine has a powerful bactericidal action. It is also active against fungi, viruses, protozoa, cysts, and spores. Potassium iodide has been used in the treatment of fungal infections such as sporotrichosis (below). Iodine is used as an **antiseptic** and **disinfectant** generally as a 2% or 2.5% solution. Its activity is reduced in the presence of organic matter, though not to the same extent as with the other halogen disinfectants. If industrial methylated spirit is used for the solution, it should be free from acetone, with which iodine forms an irritant and lachrymatory compound. Iodine solutions may be applied to small wounds or abrasions as well as to unbroken skin, but an iodophore such as povidone-iodine (p.1659) may be preferred.

Iodine may also be used to sterilise drinking water; 5 drops of a 2% alcoholic solution added to about one litre (one US quart) of water is reported to kill amoebae and bacteria within 15 minutes. Water contaminated with *Giardia* requires 12 drops of a 2% alcoholic solution for each litre which may take one hour to achieve its effect. Tablets containing tetraglycine hydroperiodide (p.1663) may be preferred.

When iodine combines chemically it is decolorised and so-called colourless iodine preparations do not have the disinfectant properties of iodine.

Iodine stains the skin a deep reddish-brown; the stain can be readily removed by dilute solutions of alkalis or sodium thiosulfate. A dilute solution of iodine (Schiller's Iodine) may also be used as a **diagnostic** stain in colposcopy.

There have been numerous other uses of iodine and iodides. Iodides have long been used as ingredients of expectorant mixtures (see Cough, p.1547) but there has been concern over their safety because of their potential for thyroid suppression. A diatomic iodine formulation is under investigation for the treatment of fibrocystic breast disease. Iodinated organic compounds including iodised oil are used as X-ray contrast media (p.1474). Potassium iodide has been given in the treatment of Sweet's syndrome (acute febrile neutrophilic dermatosis). A mixture of iodine and sodium iodide is used as sclerotherapy for varicose veins (p.2347).

Fungal infections. Potassium iodide is used in the treatment of cutaneous sporotrichosis (p.522), although how it acts is unclear since antifungal activity was not found *in vitro* against *Sporothrix schenkii*.[1] It has also been shown to be effective in the treatment of phycomycosis caused by *Basidiobolus haptosporus*[2,3] but again the mode of action is unclear.[4] Potassium iodide is usually given orally in a gradually increasing dosage up to the limit of tolerance. The WHO recommended initial dose is 1 mL [1 g] of a saturated solution of potassium iodide (1 g/mL) given three times daily; treatment should be continued for at least 1 month after the disappearance or stabilisation of the lesions.

Potassium iodide and sodium iodide have been tried by local intracavitary instillation for the treatment of life-threatening haemoptysis from pulmonary aspergillomas.[5] Mechanical factors may have accounted for a beneficial effect rather than any antifungal action. Aspergillomas are usually managed conservatively or, in more severe disease, with antifungals or surgery (see p.517).

1. WHO. *WHO model formulary.* Geneva: WHO, 2004.
2. Kelly S, *et al.* Subcutaneous phycomycosis in Sierra Leone. *Trans R Soc Trop Med Hyg* 1980; **74:** 396–7.
3. Kamalam A, Thambiah AS. Muscle invasion by Basidiobolus haptosporus. *Sabouraudia* 1984; **22:** 273–7.
4. Yangco BG, *et al.* In vitro susceptibilities of human and wild-type isolates of Basidiobolus and Conidiobolus species. *Antimicrob Agents Chemother* 1984; **25:** 413–16.
5. Rumbak M, *et al.* Topical treatment of life threatening haemoptysis from aspergillomas. *Thorax* 1996; **51:** 253–5.

Iodine deficiency disorders. Iodine is an essential trace element required for thyroid hormone production. In the UK the reference nutrient intake (RNI) for adults is 140 micrograms (1.1 micromoles) of iodine daily[1] and in the USA the recommended dietary allowance (RDA) is 150 micrograms daily.[2] A full explanation of the terms RNI and RDA can be found under Human Requirements of Vitamins, p.1925. In 1996, WHO[3] recommended the following daily iodine intakes:

- 50 micrograms up to 12 months of age
- 90 micrograms from 1 to 6 years
- 120 micrograms from 7 to 12 years
- 150 micrograms from 12 years of age
- 200 micrograms during pregnancy and lactation.

A subsequent document from the International Council for Control of Iodine Deficiency Disorders, UNICEF, and WHO recommended 90 micrograms daily for all infants and children up to 59 months of age and 120 micrograms from 6 to 12 years.[4]

When iodine requirements are not met, a range of disorders can develop. These iodine deficiency disorders include endemic goitre (enlargement of the thyroid), endemic cretinism (a syndrome characterised by deaf-mutism, intellectual deficit, spasticity, and sometimes hypothyroidism), impaired mental function in children and adults, and an increased incidence of still-births as well as perinatal and infant mortality.[3,5]

Iodine deficiency disorders can be prevented by iodine supplementation. The incidence of endemic goitre, endemic cretinism, and mental retardation can be reduced and some of the effects of established iodine deficiency ameliorated, with only modest risks.[6]

Although various methods of iodine supplementation, including iodination of sugar, water, and bread, as well as giving potassium iodide, have been investigated, the two methods generally used are iodination of culinary salt and the use of iodised oil.[3]

Salt may be iodinated by the addition of potassium iodide or potassium iodate. The concentration used in different countries varies over a wide range from 10 to about 80 ppm of elemental iodine.[4]

The chief alternative to supplementation with iodinated salt is *iodised oil*, usually by intramuscular injection; it is useful where salt consumption is unreliable or inadequate or where immediate action is necessary to correct severe iodine deficiency.[3] A commonly used type of iodised oil has been a poppyseed oil containing about 38% w/w or 480 mg/mL of iodine (see Iodised Oil, p.1482). Some countries have produced iodised oil based on alternatives such as peanut or rapeseed oil.[7,8] Single intramuscular doses can provide adequate protection from iodine deficiency for up to 3 years. WHO has recommended[9] that infants up to 1 year receive 190 mg iodine, as iodised oil (480 mg/mL iodine), by intramuscular injection; children and adults up to age 45 are given 380 mg. Subjects over the age of 45 years and those with nodular goitre are susceptible to hyperthyroidism when given iodine, and iodised oil may not be a suitable means of supplementation. If it is used, doses of 76 mg are given.[9]

Iodised oil may also be given orally once yearly. WHO recommends[9] that infants up to 1 year be given a single dose of 100 mg iodine, children from 1 to 5 years 200 mg, and those over 6 years 400 mg. The evidence suggests that oral iodised oil is as effective as intramuscular for preventing iodine deficiency disorders in children.[10] Adults are also given 400 mg, except during pregnancy, when a single dose of 200 mg is recommended.[9]

Iodine or iodides may suppress neonatal thyroid function and it is generally recommended that iodine compounds should be avoided during **pregnancy**. However, where it is essential to prevent neonatal goitre and cretinism, iodine supplementation should not be withheld from pregnant women.[11,12] Iodine supplementation has been found to be effective in preventing brain-damage in the fetus provided it is given to the mother in the first or second trimester;[11] treatment later in pregnancy was not effective in improving neurological status, although some developmental improvement was seen and hypothyroidism will be corrected. WHO has stated that in areas where iodine deficiency disorders are moderate to severe, iodised oil given either before or at any stage of gestation is beneficial.[9,12] A dose of 480 mg iodine intramuscularly each year, or 300 to 480 mg iodine by mouth each year, or 100 to 300 mg iodine by mouth every 6 months, is recommended for pregnant women and for at least one year postpartum. Similar intramuscular doses are recommended for non-pregnant fertile women with oral doses being 400 to 960 mg iodine every year, or 200 to 480 mg every 6 months.[9]

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.

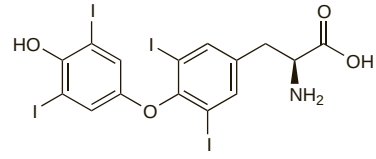
Левотироксин Натрий

$C_{15}H_{10}I_4NNaO_4.xH_2O$ = 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-