

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adverse effects, especially cardiac complications.¹ Hypothyroidism has also been reported² when these drugs were withdrawn from previously euthyroid patients being treated for simple obesity.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. Rumblyrt 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 Invest 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.:** Eutroxisig; Oroxine; **Austria:** Euthyrox; Neothyron; Thyrex; **Belg.:** Elthyron; Euthyrox; Thyra; **Braz.:** Euthyrox; Puran T4; Synthroid; Tetroid; Tiroidin; **Canad.:** Eltroxin; Euthyrox; Synthroid; **Chile:** Esaldox; Eutirox; **Cz.:** Eltroxin; Euthyrox; Letrox; Thyra†; **Denm.:** Eltroxin; **Fr.:** Levothyrox; **Ger.:** Berlthyrox; Eferox; Euthyrox; L-Thyrox; Lixin; Thievier; **Gr.:** Levothyroid; T-4; Thyro-4; Thyrohormone; **Hong Kong:** Eltroxin; **Hung.:** Euthyrox; Letrox; **India:** Eltroxin; **Indon.:** Euthyrox; Thyra; **Irl.:** Eltroxin; **Israel:** Eltroxin; **Ital.:** Eutirox; Tiracin; Tiro-sint; **Jpn.:** Thyradin-S; **Malaysia:** Oroxine; **Mex.:** Abutiro; Cynocuatro; Daltroid†; Eutirox; Sintrocid†; **Tiroidine; Neth.:** Eltroxin; Euthyrox; Thyra; **Norw.:** Levaxin; **NZ:** Eltroxin; **Philipp.:** Eltroxin; Euthyrox; Thyra; Thyrohex; **Pol.:** Eferox; Eltroxin; Euthyrox; Oroxine; **Spain:** Dexton; Eutirox; Levothyroid; **Swed.:** Euthyrox; Levaxin; **Switz.:** Eltroxin; Euthyrox; **Thai.:** Elthyro; Eltroxin; Euthyrox; Pondtroxin; Thyrosit; **Turk.:** Levotiron; Tefor; **UK:** Eltroxin; Evotrox; **USA:** Levothyroid; Levoxyl; Novothyrox; Synthroid; Unithroid; **Venez.:** Euthyrox; Thyra.

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 (ТиреокOMB); Thyreotom (Тиреотом); **S.Afr.:** Diotroxin; **Switz.:** Novothyral; **Turk.:** Bitiron; **USA:** Thyrolar.

Liothyronine Sodium (BANM, rINNM)

Liothyronin sodná sůl; Liothyronine sodique; Liothyroninum natrium; Liotironin Sodyum; Liotironina sódica; Liotironin-nátrium; Liotironina natrio druska; Liotironiniinatrium; Liotironina sod-ova; Liotironinnatrium; Natrii Liothyroninum; Sodyum 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.

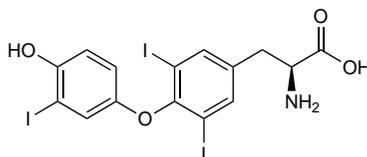
Натрий Лиотиронин

C₁₅H₁₁I₃NNaO₄ = 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 T₃ 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.: Tetroxin; **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.:** Tiroimel; **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.:** Ney/Normin N (Revitorgan-Dilutionen N Nr 65)†; Ney/Tumorin 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 (ТиреокOMB); Thyreotom (Тиреотом); **S.Afr.:** Diotroxin; **Switz.:** Novothyral; **Turk.:** Bitiron; **USA:** Thyrolar.

Potassium Perchlorate

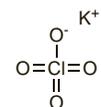
Chloristan draselny; Kalii perchloras; Kalio perchloratas; Kaliumperchloraat†; Kaliumperchlorat; Kálium-perchlorát; Perchlorato potásico; Potassium, perchlorate de.

KClO₄ = 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.

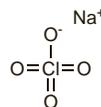
USP 31 (Potassium Perchlorate). pH of a 0.1M solution in water is between 5.0 and 6.5.

Sodium Perchlorate

Perchlorato sódico; Sodu naddchloran.

NaClO₄ = 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

associated with serious dose-related adverse effects. Aplastic anaemia (with some fatalities), agranulocytosis, leucopenia, pancytopenia, and the nephrotic syndrome have been reported. Excessive doses may cause hypothyroidism and goitre.

Effects on the blood. There have been reports of fatal aplastic anaemia^{1,2} and of leucopenia and agranulocytosis¹ associated with the use of potassium perchlorate for the treatment of hyperthyroidism. A review³ in 1998 noted that despite an increase in perchlorate use in recent years there did not appear to have been any further cases of aplastic anaemia since the 1960s.

1. Anonymous. Potassium perchlorate and aplastic anaemia. *BMJ* 1961; **i**: 1520-1.
2. Krevans JR, et al. Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. *JAMA* 1962; **181**: 182-4.
3. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50**: 89-105.

Uses and Administration

Potassium and sodium perchlorate reduce the uptake and concentration of iodide, perchlorate, and other anions by the thyroid, choroid plexus, gastric mucosa, and salivary glands, probably by competitive inhibition of active transport mechanisms.

They are used **diagnostically** as adjuncts to perchlorate (^{99m}Tc) to enhance visualisation of the brain, Meckel's diverticulum, or the placenta by reducing unwanted images of other organs. The usual oral dose of either potassium or sodium perchlorate is 200 to 400 mg given 30 to 60 minutes before the use of sodium perchlorate (^{99m}Tc).

Potassium and sodium perchlorate are also used with sodium iodide (¹³¹I) in the perchlorate discharge test of thyroid function. The release of radio-iodine from the gland following an oral dose of perchlorate indicates a defect in the binding of iodide by the thyroid and thus a defect in thyroid hormone synthesis. The test has also been used to investigate the action of antithyroid drugs. Potassium and sodium perchlorate have been used in the treatment of **hyperthyroidism** (p.2165), but because of toxicity have been largely replaced by alternative treatments. However, perchlorates may be useful in patients with iodine-induced hyperthyroidism such as that associated with amiodarone therapy, by increasing responsiveness to conventional antithyroid drugs. A typical dose of potassium perchlorate in amiodarone-induced hyperthyroidism is 1 g daily.

References

1. Bartalena L, et al. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. *J Clin Endocrinol Metab* 1996; **81**: 2930-3.
2. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50**: 89-105.
3. Soldin OP, et al. Perchlorate clinical pharmacology and human health: a review. *Ther Drug Monit* 2001; **23**: 316-31.
4. Bartalena L, et al. Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; **61**: 494-502.

Preparations

USP 31: Potassium Perchlorate Capsules.

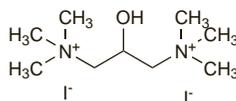
Proprietary Preparations (details are given in Part 3)

Austria: Irenat; **Cz.:** Irenat; **Ger.:** Irenat; **Ital.:** Pertiroid; **Pol.:** Irenat; **USA:** Perchloracap†.

Prolonium Iodide (rINN)

Ioduro de prolonio; Prolonii Iodidum; Prolonium, Iodure de. *NN*-2-Hydroxytrimethylene)bis(trimethylammonium) di-iodide.

Пролония Йодид
C₉H₂₄I₂N₂O = 430.1.
CAS — 123-47-7.



Pharmacopoeias. In *Chin.*

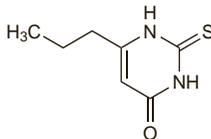
Profile

Prolonium iodide has been given by injection as a source of iodine (p.2169) as part of the treatment of thyroid storm and for the pre-operative management of hyperthyroidism.

Propylthiouracil (BAN, rINN)

Proiltiourasil; Propiltiouracil; Propiltiouracilas; Propiltiouracilo; Propylthiouracile; Propylthiouracilum; Propylthiouracil; Propylthiouracilum. 2,3-Dihydro-6-propyl-2-thioxopyrimidin-4(1H)-one; 2-Mercapto-6-propylpyrimidin-4-ol; 6-Propyl-2-thiouracil.

Пропиатиурацил
C₇H₁₀N₂O₂ = 170.2.
CAS — 51-52-5.
ATC — H03BA02.
ATC Vet — QH03BA02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn.*, and *US*. **Ph. Eur. 6.2** (Propylthiouracil). White or almost white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.

USP 31 (Propylthiouracil). A white, powdery, crystalline substance. It is starch-like in appearance and to the touch. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol; soluble in ammonium hydroxide and in alkali hydroxides. Protect from light.

Adverse Effects and Precautions

As for Carbimazole, p.2167, although cross-sensitivity to carbimazole does not necessarily occur.

Propylthiouracil has been associated with greater hepatotoxicity than other thiourea antithyroid drugs (such as carbimazole or thiamazole). Rarely hepatitis, hepatic necrosis, encephalopathy, and death have occurred; asymptomatic liver damage is more common (see Effects on the Liver, under Carbimazole, p.2168).

Propylthiouracil should be given with care, and in reduced doses, to patients with renal impairment.

Breast feeding. Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily, see Breast Feeding, under Carbimazole, p.2167.

Pharmacokinetics

Propylthiouracil is rapidly absorbed from the gastrointestinal tract with a 50 to 75% bioavailability and with peak plasma concentrations occurring about 2 hours after oral doses. It is concentrated in the thyroid gland; since its duration of action is more closely related to the intrathyroidal drug concentration than its plasma half-life, prolonged antithyroid activity results from single daily doses. Propylthiouracil is about 80% bound to plasma proteins.

Propylthiouracil has an elimination half-life of about 1 to 2 hours. It undergoes rapid first-pass metabolism in the liver, and is mainly excreted in the urine as the glucuronic acid conjugate, with less than 2% excreted as unchanged drug. The elimination half-life may be increased in renal or hepatic impairment.

Propylthiouracil crosses the placenta and is distributed into breast milk.

Uses and Administration

Propylthiouracil is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p.2165); it also inhibits the peripheral deiodination of thyroxine to tri-iodothyronine. It is used in the management of hyperthyroidism (p.2165), including the treatment of Graves' disease, preparation of hyperthyroid patients for thyroidectomy, use as an adjunct to radio-iodine therapy, and the treatment of thyroid storm.

Propylthiouracil is usually given orally. Initial doses range from 150 to 450 mg daily (the *BNF* recommends 200 to 400 mg daily), although in severe cases initial doses of 600 to 1200 mg daily have been used. It has often been given in divided daily doses but once daily dosage is also possible. Improvement is usually seen in 1 to 3 weeks and control of symptoms is achieved in 1 to 2 months. When the patient is euthyroid the dose is

gradually reduced to a maintenance dose, usually 50 to 150 mg daily. Treatment is usually continued for 1 to 2 years. In the UK, the *BNFC* recommends the following initial doses by mouth for children:

- in neonates: 2.5 to 5 mg/kg twice daily
- in those aged 1 month to 1 year: 2.5 mg/kg three times daily
- in those aged 1 to 5 years: 25 mg three times daily
- in those aged 5 to 12 years: 50 mg three times daily
- in those aged 12 to 18 years: 100 mg three times daily

These doses are given until the patient is euthyroid and then adjusted as needed; higher doses may be required, especially in thyrotoxic crises.

Doses should be reduced in renal impairment (below). Doses may also need to be reduced in hepatic impairment.

Administration in renal impairment. The dosage of propylthiouracil should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

- CC 10 to 50 mL/minute, doses should be reduced by 25%
- CC less than 10 mL/minute, reduce doses by 50%

Alcoholic liver disease. Propylthiouracil has been said to reduce hyperoxic liver injury in hypermetabolic *animals* and despite reports of hepatotoxicity, including some fatalities, associated with propylthiouracil (see Effects on the Liver, under Carbimazole, p.2168), it has been investigated in the treatment of patients with alcoholic liver disease. A systematic review¹, however, concluded that there is no evidence to substantiate this use. Propylthiouracil was associated with adverse effects and it could not be shown to have any significant effects on mortality, liver related mortality, liver complications, and liver histology.

1. Rambaldi A, Gluud C. Propylthiouracil for alcoholic liver disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 01/08/08).

Psoriasis. Several reports have described benefit in patients with psoriasis (p.1583) given propylthiouracil. An oral dose of 300 mg daily for 8 to 12 weeks has been used and is said not to produce clinical hypothyroidism.¹

1. Elias AN. Anti-thyroid thioureylenes in the treatment of psoriasis. *Med Hypotheses* 2004; **62**: 431-7.

Preparations

BP 2008: Propylthiouracil Tablets;

USP 31: Propylthiouracil Tablets.

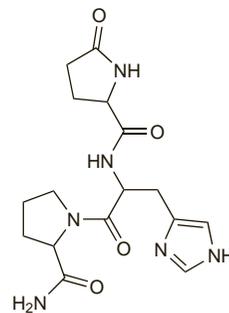
Proprietary Preparations (details are given in Part 3)

Austria: Prothiuracil; **Braz.:** Propil; Propilracil; **Canad.:** Propyl-Thiuracil; **Cz.:** Propycil; **Ger.:** Propycil; Thyreostat; **Gr.:** Prothuriol; **Hong Kong:** CP-PTU; **Hung.:** Propycil; **Israel:** Propylthiuracil; **Pol.:** Thyrosan; **Port.:** Propycil; **Swed.:** Tiotil; **Switz.:** Propycil; **Thai.:** Propyl; Uracl; **Turk.:** Propycil.

Protirelin (BAN, USAN, rINN)

Abbott-38579; Lopremone; Protireliini; Protirelina; Protirelinas; Protiréline; Protirelinum; Synthetic TRH; Thyrotrophin-releasing Hormone; Thyrotrophin-releasing Hormone; TRF; TRH. L-Pyrroglutamyl-L-histidyl-L-prolinamide; 1-[N-(5-Oxo-L-prolyl)-L-histidyl]-L-prolinamide; Glu-His-Pro-NH₂.

Протирелин
C₁₆H₂₂N₆O₄ = 362.4.
CAS — 24305-27-9.
ATC — V04CJ02.
ATC Vet — QV04CJ02.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*, which also includes the tartrate.

Ph. Eur. 6.2 (Protirelin). A synthetic tripeptide with the same sequence of amino acids as the natural hypothalamic neurohormone, that stimulates the release and synthesis of thyrotrophin.