has been applied, alone or with other drugs, for its supposed anti-inflammatory properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Mex.: Cro 50.

Multi-ingredient: ***Braz.:*** Bromelin†; Expectoral†; ***Fr.:*** Ribatran; ***Mex.:*** Ofzim; Ridasa.

Ribonucleic Acid

ARN; Plant Nucleic Acid; Ribonucleico, ácido; Ribose Nucleic Acid; RNA; Yeast Nucleic Acid.

Рибонуклеиновая Кислота

Profile

Ribonucleic acid (RNA) is a nucleic acid (p.2355) in which the pentose sugar moiety of the nucleotides is ribose, the purine bases are adenine (p.2247) and guanine, and the pyrimidine bases are cytosine and uracil (p.2407). RNA exists as a single polynucleotide strand that replicates using DNA as a template during which process the pairing of bases between the complementary strands of RNA and DNA is always the same: adenine with uracil and cytosine with guanine. RNA is present in cell nuclei and cytoplasm and is directly involved in protein synthesis; it also plays a part in encoding genetic information. RNA also carries the genetic material of RNA viruses. Gene suppression by RNA interference (RNAi), using specific double-stranded ribonucleic acid sequences, is under investigation. For the role of RNA as a tool in gene therapy, see p.2310.

Proprietary preparations containing RNA are marketed in some countries for a variety of asthenic and convalescent conditions. RNA has also been tried in the treatment of mental retardation and to improve memory in senile dementia. It may also have a role in enteral feeds under some circumstances.

Immune RNA (extracted from the spleens and lymph nodes of immunised animals) has been tried in the immunotherapy of hepatitis and cancer.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: AU 4 Regeneresen; Osteochondrin S; Regeneresen; RN13 Regeneresen.

Multi-ingredient: ***India:*** Placentrex; ***Spain:*** Dertrase; Nucleserina; Policolinosil.

Ribwort Plantain

Heinäratamonlehti; Jitrocelový list; Liść babki lancetowatej; Plantaginis Folium; Plantaginis Lanceolatae; Plantaginis lanceolatae folium; Plantain Herb; Plantain lancéolé; Siauralapių gysločių lapai; Spitzwegerich; Spitzwegerichkraut; Svartkämparblad.

Pharmacopoeias. *Eur.* (see p.vii) includes the leaf.
Ph. Eur. 6.2 (Ribwort Plantain; Plantaginis Lanceolatae Folium). The whole or fragmented, dried leaf and scape of *Plantago lanceolata*. It contains not less than 1.5% of total *ortho*-dihydroxycinnamic acid derivatives expressed as acteoside ($C_{29}H_{36}O_{15}$ = 624.6) with reference to the dried drug. Protect from light.

Profile

Ribwort plantain is an ingredient in herbal remedies used for catarrh and inflammation of the upper respiratory tract.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Jitrocel v Nalevovych†; Jitrocelovy; ***Fr.:*** Sensivision au plantain; ***Ger.:*** Broncho-Sern; Proguval†; Tetesept Husten Saft; Tetesept Husten Tropfen; ***Pol.:*** Lancetan; Lanceticum; Plantagen.

Multi-ingredient: ***Austria:*** Brust- und Hustentee St Severin; Grippetee St Severin; Pneumopan; Scottopect; ***Canad.:*** Original Herb Cough Drops; ***Cz.:*** Biotussil; Bronchialtee N†; Cajova Smes pri Nachlazeni; Detsky Caj s Hermankem; Dr Theiss Spitzwegerich Hustensaft†; Mucoplant Jitrocelovy; Naturident†; Prudušková; Pulmoran; Species Pectorales Planta; Thymomel; ***Ger.:*** Bronchicum Elixir Plus†; Equisil N; Eucabal†; Kneipp Husten- und Bronchial-Tee; ***Hong Kong:*** Pectoral†; ***Ital.:*** Altea (Specie Composta)†; Timo (Specie Composta)†; ***Pol.:*** Babicum; Echinasal; Flegatussin; Gwajatussin; Pectobonisol; Plantifort; Saponarex; ***Rus.:*** Eucabal (Эвкабал); Herbion Plantain Syrup (Гербион Сироп Подорожника); Stoptussin-Fito (Стоптуссин-фито); ***Spain:*** Llantusil†; Natusor Farinol†; Natusor Gastrolen†; Natusor Infenol†; ***Switz.:*** Bronchofluid N†; Gouttes contre la toux "S"; Neo-DP†; Nican; Pastilles bronchiques S nouvelle formule; Thymodrosin N†; Wala Pulmonium suc contre la toux.

Ricin

Ricino.

CAS — 9009-86-3.

NOTE. The title ricin is used for the castor seed in *Chin.* and *Fr.*

Profile

Ricin is a lectin present in castor seeds, the seeds of *Ricinus communis* (Euphorbiaceae). It is extremely toxic when given parenterally and the fatal dose by injection has been reported to be around 1 microgram/kg. The toxicity of orally ingested beans depends on how thoroughly they are chewed since the hard seed coat prevents absorption. Ingestion of as few as 3 castor seeds by a child and 4 by an adult may be fatal. Ricin may also be absorbed through abraded skin. It has potential use in aerosol form as an agent of chemical warfare. Toxic effects may be delayed for several days after exposure by any route. Early symptoms include severe gastrointestinal irritation, haemorrhage, vomiting, and diarrhoea, which may result in circulatory collapse. Abnormal liver function tests and pulmonary oedema have been reported. Ophthalmological disturbances ranging from irritation and conjunctivitis to optic nerve damage may occur; miosis and mydriasis have also been reported. Proteinuria, haematuria, and renal impairment may develop and serum creatinine levels may be raised. In severe cases haemolysis of the red blood cells with subsequent acute renal failure may occur. Fatalities due to multi-organ failure have occurred. If the patient presents within 1 hour of ingestion any seeds may be removed by gastric lavage and activated charcoal given. Treatment thereafter is symptomatic.

After expression of the oil from castor seeds (see p.2278), the ricin remaining in the seed cake or 'pomace' is destroyed by steam treatment. The detoxified pomace is used as a fertiliser.

Ricin conjugated with monoclonal or polyclonal antibodies is being studied in the treatment of cancers; zolimomab aritox is an example of such a conjugate. Some of these conjugates have been investigated for various malignancies, particularly leukaemias and lymphomas.

Toxicity. A report of ricin toxicity after partial chewing and ingestion of 10 to 15 castor oil seeds,[1] and reviews[2-4] of ricin toxicity, including its potential as an agent of chemical warfare.

1. Aplin PJ, Eliseo T. Ingestion of castor oil plant seeds. *Med J Aust* 1997; **167:** 260–1.
2. Bradberry SM, *et al.* Ricin poisoning. *Toxicol Rev* 2003; **22:** 65–70.
3. Lord MJ, *et al.* Ricin: mechanisms of cytotoxicity. *Toxicol Rev* 2003; **22:** 53–64.
4. Audi J, *et al.* Ricin poisoning: a comprehensive review. *JAMA* 2005; **294:** 2342–51.

Uses. References to the use of ricin conjugates with monoclonal antibodies in the treatment of cancer.

1. Byers VS, *et al.* Phase I study of monoclonal antibody-ricin A chain immunotoxin XomaZyme-791 in patients with metastatic colon cancer. *Cancer Res* 1989; **49:** 6153–60.
2. Oratz R, *et al.* Antimelanoma monoclonal antibody-ricin A chain immunoconjugate (XMMME-001-RTA) plus cyclophosphamide in the treatment of metastatic malignant melanoma: results of a phase II trial. *J Biol Response Mod* 1990; **9:** 345–54.
3. Anonymous. Application considered for immunotoxin in treatment of graft-vs-host disease. *JAMA* 1991; **265:** 2041–2.
4. Amlot PL, *et al.* A phase I study of an anti-CD22-deglycosylated ricin A chain immunotoxin in the treatment of B-cell lymphomas resistant to conventional therapy. *Blood* 1993; **82:** 2624–33.
5. Senderowicz AM, *et al.* Complete sustained response of a refractory, post-transplantation, large B-cell lymphoma to an anti-CD22 immunotoxin. *Ann Intern Med* 1997; **126:** 882–5.
6. Multani PS, *et al.* Phase II clinical trial of bolus infusion anti-B4 blocked ricin immunoconjugate in patients with relapsed B-cell non-Hodgkin's lymphoma. *Clin Cancer Res* 1998; **4:** 2599–2604.
7. Dinndorf P, *et al.* Phase I trial of anti-B4-blocked ricin in pediatric patients with leukemia and lymphoma. *J Immunother* 2001; **24:** 511–16.
8. Schnell R, *et al.* Clinical evaluation of ricin A-chain immunotoxins in patients with Hodgkin's lymphoma. *Ann Oncol* 2003; **14:** 729–36.
9. Tsimberidou AM, *et al.* Anti-B4 blocked ricin post chemotherapy in patients with chronic lymphocytic leukemia—long-term follow-up of a monoclonal antibody-based approach to residual disease. *Leuk Lymphoma* 2003; **44:** 1719–25.

Ricinoleic Acid

Kwas rycynolowy; Ricinoleico, ácido.

CAS — 141-22-0.

Profile

Ricinoleic acid is a mixture of fatty acids obtained by the hydrolysis of castor oil. It is an ingredient of some proprietary vaginal jellies used to maintain or restore normal vaginal acidity.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Austral.:*** Aci-Jel†; ***Israel:*** Glovan; ***NZ:*** Aci-Jel†; ***USA:*** Acid Jelly.

Rilonacept *(USAN, rINN)*

IL-1 Trap; Interleukin-1 Receptor; Interleukin-1 Trap; Rilonaceptum.

Рильонацепт

CAS — 501081-76-1.

Profile

Rilonacept is an interleukin-1 blocker used in the treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold auto-inflammatory syndrome (FCAS) and Muckel-Wells syndrome (MWS), which are rare inherited auto-inflammatory disorders. Rilonacept is a soluble decoy interleukin-1 receptor that binds interleukin-1_{beta} (p.2325) and blocks its actions at cell surfaces.

Rilonacept is given by subcutaneous injection. The solution, when prepared according to the manufacturer's directions, contains 160 mg per 2 mL and this is the maximum amount that should be given as a single injection or at a single site; if a larger dose is required (as at loading) two separate injections should be given on the same day at two different sites.

The loading dose is 320 mg (as two separate injections). A single injection of 160 mg is then given once weekly. The loading dose for children aged 12 to 17 years is 4.4 mg/kg up to a maximum of 320 mg (given as one or two injections depending on the dose). A single injection of 2.2 mg/kg up to a maximum of 160 mg is then given once weekly.

Preparations

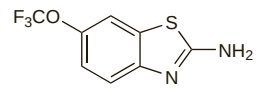
Proprietary Preparations (details are given in Part 3)
USA: Arcalyst.

Riluzole *(BAN, USAN, rINN)*

PK-26124; Rilutsoli; Riluzol; Riluzolum; RP-54274. 2-Amino-6-(trifluoromethoxy) benzothiazole; 6-Trifluoromethoxy-1,3-benzothiazol-2-ylamine.

Рилузол

$C_8H_5F_3N_2OS$ = 234.2.
CAS — 1744-22-5.
ATC — N07XX02.
ATC Vet — QN07XX02.



Adverse Effects and Treatment

Adverse effects associated most commonly with riluzole are asthenia, nausea, elevations in liver enzyme values, headache, and abdominal pain. Other gastrointestinal effects may include diarrhoea or constipation, anorexia, and vomiting. There may be tachycardia, dizziness, vertigo, or somnolence. Circumoral paraesthesia has been reported and decreased lung function and rhinitis may occur. Anaphylactoid reactions, angioedema, pancreatitis, and neutropenia have all been reported rarely.

Effects on the blood. Severe neutropenia has been reported[1] in a 71-year old patient with amyotrophic lateral sclerosis receiving standard doses of riluzole. The neutrophil count returned to normal on cessation of riluzole.

See also under Overdosage, below.

1. Weber G, Bitterman H. Riluzole-induced neutropenia. *Neurology* 2004; **62:** 1648.

Effects on the kidneys. A 44-year-old patient developed renal tubular impairment 3 months after starting riluzole for amyotrophic lateral sclerosis.[1] Tubular function recovered 1 month after stopping riluzole.

1. Poloni TE, *et al.* Renal tubular impairment during riluzole therapy. *Neurology* 1999; **52:** 670.

Effects on the liver. Icteric toxic hepatitis, with jaundice and elevated liver enzyme values, has been reported[1] in an elderly woman receiving riluzole for amyotrophic lateral sclerosis (ALS). Acute hepatitis developed in 2 patients several weeks after starting therapy with riluzole for ALS.[2] Liver histology showed hepatocellular damage with inflammatory infiltration and microvesicular steatosis without fibrosis. Hepatotoxicity was reversed in all these cases when riluzole was stopped.

1. Castells LI, *et al.* Icteric toxic hepatitis associated with riluzole. *Lancet* 1998; **351:** 648.
2. Remy A-J, *et al.* Acute hepatitis after riluzole administration. *J Hepatol* 1999; **30:** 527–30.

Effects on the pancreas. Riluzole was cited[1] as the most likely cause of severe pancreatitis that developed in a 77-year-old woman 6 months after starting therapy for sporadic amyotrophic lateral sclerosis; pancreatic symptoms improved when riluzole was stopped.

1. Drory VE, *et al.* Riluzole-induced pancreatitis. *Neurology* 1999; **52:** 892–3.

Hypersensitivity. A severe life-threatening systemic inflammatory reaction occurred in a patient 2 weeks after starting treatment with riluzole for amyotrophic lateral sclerosis.[1] Symptoms resolved spontaneously on stopping riluzole.

1. Sorenson EJ. An acute, life-threatening, hypersensitivity reaction to riluzole. *Neurology* 2006; **67:** 2260–1.

Overdosage. Severe neutropenia developed in a 63-year-old woman receiving riluzole for amyotrophic lateral sclerosis 10 days after inadvertent dose increase to 200 mg daily (twice the standard recommended dose).[1]

Methaemoglobinaemia has been reported[2] in a 43-year-old patient with amyotrophic lateral sclerosis after intentional overdose with 2.8 g of riluzole. The patient was treated with gastric lavage followed by activated charcoal; intravenous methylthioninium chloride successfully reversed the methaemoglobinaemia. However, the patient died of respiratory failure related to her underlying disease 7 days after the overdose.

An amnesic syndrome that persisted for over a year developed in a woman 4 days after ingestion of 3 g of riluzole.[3]

1. North WA, *et al.* Reversible granulocytopenia in association with riluzole therapy. *Ann Pharmacother* 2000; **34:** 322–4.

2. Viallon A, *et al.* Methemoglobinemia due to riluzole. *N Engl J Med* 2000; **343:** 665–6.
3. Haaxma CA, *et al.* Delayed amnesic syndrome after riluzole autointoxication in Huntington disease. *Neurology* 2006; **66:** 1123–4.

Precautions

Riluzole is contra-indicated in patients with hepatic disease or markedly raised liver enzyme values. Liver function tests should be performed before and throughout treatment with riluzole. In the UK, riluzole is not recommended in patients with renal impairment although US licensed product information states that the pharmacokinetics are not significantly different in renal impairment. Caution should be exercised in those with a history of liver disorders. Patients or their carers should be told how to recognise signs of neutropenia and should be advised to seek immediate medical attention if symptoms such as fever develop; white blood cell counts should be determined in febrile illness and riluzole stopped if neutropenia occurs. Riluzole may cause dizziness or vertigo and patients should be warned not to drive or operate machinery if these symptoms occur.

Riluzole has been reported to impair fertility in *animals*.

Pharmacokinetics

Riluzole is rapidly absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations occurring in 1 to 1½ hours. The rate and extent of absorption are decreased when riluzole is given with a high-fat meal. Riluzole is widely distributed throughout the body and is about 97% bound to plasma proteins. It crosses the blood-brain barrier. Riluzole is extensively metabolised to several metabolites in the liver, mainly by the cytochrome P450 isoenzyme CYP1A2, and subsequent glucuronidation. Riluzole is excreted mainly in the urine, mainly as glucuronides, with an elimination half-life of about 9 to 15 hours. About 2% is excreted unchanged in the urine. Small amounts are excreted in faeces. There is some evidence that clearance of riluzole is reduced in Japanese patients.

◊ References.

1. Le Liboux A, *et al.* Single- and multiple-dose pharmacokinetics of riluzole in white subjects. *J Clin Pharmacol* 1997; **37:** 820–7.
2. Le Liboux A, *et al.* A comparison of the pharmacokinetics and tolerability of riluzole after repeat dose administration in healthy elderly and young volunteers. *J Clin Pharmacol* 1999; **39:** 480–6.
3. Groeneveld GJ, *et al.* Riluzole serum concentrations in patients with ALS: associations with side effects and symptoms. *Neurology* 2003; **61:** 1141–3.
4. van Kan HJ, *et al.* Association between CYP1A2 activity and riluzole clearance in patients with amyotrophic lateral sclerosis. *Br J Clin Pharmacol* 2005; **59:** 310–13.

Uses and Administration

Riluzole is a glutamate antagonist used in the management of amyotrophic lateral sclerosis, a form of motor neurone disease. Riluzole is indicated to slow progression of early disease but efficacy has not been demonstrated in its late stages. The precise mechanism of action is unknown but it may inhibit presynaptic glutamate release and interfere with its postsynaptic effects. The usual adult dose of riluzole is 50 mg twice daily by mouth on an empty stomach.

Motor neurone disease. Motor neurone disease (motoneuron disease) represents a group of fatal progressive degenerative disorders that affect upper and/or lower motor neurones in the brain and spinal cord. The most common form of motor neurone disease is amyotrophic lateral sclerosis (known in the USA as Lou Gehrig's disease), which involves both upper and lower motor neurones. It produces muscular atrophy and weakness and symptoms of progressive bulbar palsy such as slowness of movement and speech disturbances. Most patients die within 2 to 5 years of disease onset, usually from respiratory failure. There is no completely effective treatment and management remains largely supportive with appropriate symptomatic management of spasticity (p.1887), pain (p.8), and sialorrhoea. Tricyclic antidepressants are widely used for their multiple beneficial effects. Occupational and speech therapy also play a crucial role in maximising function. Pathological crying or laughing (pseudobulbar affect) may occur in as many as 50% of patients and has been treated with amitriptyline or fluvoxamine. Dysphagia may eventually compromise food and fluid intake necessitating enteral nutrition as an alternative or supplemental route for oral nutrition. Respiratory support will ultimately be necessary, initially with non-invasive ventilation but progressing eventually to tracheostomy.

Although the pathogenesis of motor neurone disease is still uncertain, it is thought that accumulation of the excitatory neurotransmitter glutamate in the CNS may be involved. Clinical studies have shown riluzole, a glutamate antagonist, to be modestly effective in prolonging survival by an average of 3 months and delaying the time to use of tracheostomy. However, there is still insufficient data to be able to assess which patients would derive greatest benefit. Additionally, questions have been raised about the clinical usefulness of riluzole in terms of cost-benefit, and there are concerns about adverse effects, notably hepatotoxicity.

Also under study for the treatment of motor neurone disease are somatomedins, in particular mecasermin (insulin-like growth factor I). Neurotrophic factors have been investigated including brain-derived neurotrophic factor (BDNF) and recombinant ciliary neurotrophic factor (CNTF), but results have been generally inconclusive. Glial-cell-derived neurotrophic factor (GDNF) and xaliproden are under investigation.

There has been some interest in the antiepileptic drug gabapentin, which may inhibit glutamate formation in the CNS from branched-chain amino acids. Lamotrigine and topiramate have also been tried but with disappointing results. ONO-2506 is an enantiomeric homologue of valproate that is also under investigation. Dextromethorphan has been studied in amyotrophic lateral sclerosis. Minocycline has demonstrated neuroprotective effects in *animal* studies and is therefore also being studied in this condition; ceftriaxone is also under investigation. Immunoglobulins have been tried in some forms of motor neurone disease such as multifocal motor neuropathy.

Antoxidants, including vitamins C and E, are commonly used by patients in the belief that one mechanism for neuronal death is free radical accumulation resulting from oxidative stress. However, despite substantial literature on the subject and widespread use of antoxidants, significant evidence to support their benefit in motor neurone disease is lacking. Creatine supplements have been tried in a bid to preserve motor function and motor neurones, although benefit has not been shown in controlled studies.

A small percentage of patients with familial amyotrophic lateral sclerosis has been shown to have a mutation in the gene encoding for the enzyme copper-zinc superoxide dismutase but there has been no consensus as to whether patients with this mutation should be given superoxide dismutase supplements.

References.

1. Ludolph AC, Riepe MW. Do the benefits of currently available treatments justify early diagnosis and treatment of amyotrophic lateral sclerosis? — Arguments against. *Neurology* 1999; **53** (suppl 5): S46–S49.
2. Cashman NR. Do the benefits of currently available treatments justify early diagnosis and announcement? — Arguments for. *Neurology* 1999; **53** (suppl 5): S50–S52.
3. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001; **344:** 1688–1700.
4. Dib M. Amyotrophic lateral sclerosis: progress and prospects for treatment. *Drugs* 2003; **63:** 289–310.
5. Leigh PN, *et al.* The management of motor neurone disease. *J Neurol Neurosurg Psychiatry* 2003; **74** (suppl 4): iv32–iv47.
6. Ashworth NL, *et al.*. Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 28/04/06).
7. Choudry RB, Cudkowicz ME. Clinical trials in amyotrophic lateral sclerosis: the tenuous past and the promising future. *J Clin Pharmacol* 2005; **45:** 1334–44.
8. Traynor BJ, *et al.* Neuroprotective agents for clinical trials in ALS: a systematic assessment. *Neurology* 2006; **67:** 20–7.
9. Miller RG, *et al.* Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
10. Orrell RW, *et al.* Antioxidant treatment for amyotrophic lateral sclerosis / motor neuron disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 17/06/08).
11. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *Lancet* 2007; **369:** 2031–41.
12. Mitsumoto H, Rabkin JG. Palliative care for patients with amyotrophic lateral sclerosis: prepare for the worst and hope for the best. *JAMA* 2007; **298:** 207–16.
13. McDermott CJ, Shaw PJ. Diagnosis and management of motor neurone disease. *BMJ* 2008; **336:** 658–62.
14. Corcia P, Meininger V. Management of amyotrophic lateral sclerosis. *Drugs* 2008; **68:** 1037–48.

Movement disorders. Beneficial results have been obtained with riluzole in small studies of patients with Huntington's chorea.[1,2] Riluzole has been tried in a small number of patients with early Parkinson's disease but no evidence of benefit was observed.[3] It has also been tried in levodopa-induced dyskinesias in advanced Parkinson's disease with conflicting reports of benefit[4] or no benefit.[5]

1. Rosas HD, *et al.* Riluzole therapy in Huntington's disease (HD). *Mov Disord* 1999; **14:** 326–30.
2. Huntington Study Group. Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study. *Neurology* 2003; **61:** 1551–6.
3. Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease. *Parkinsonism Relat Disord* 2002; **8:** 271–6.
4. Merims D, *et al.* Riluzole for levodopa-induced dyskinesias in advanced Parkinson's disease. *Lancet* 1999; **353:** 1764–5.
5. Braz CA, *et al.* Effect of riluzole on dyskinesia and duration of the ON state in Parkinson disease patients: a double-blind, placebo-controlled pilot study. *Clin Neuropharmacol* 2004; **27:** 25–9.

Psychiatric disorders. Glutamate is implicated in the aetiology of various psychiatric disorders and consequently riluzole has been suggested as a potential treatment in view of its glutamate-modulating properties.

References.

1. Zarate CA, *et al.* An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry* 2004; **161:** 171–4.
2. Sanacora G, *et al.* Riluzole augmentation for treatment-resistant depression. *Am J Psychiatry* 2004; **161:** 2132.
3. Zarate CA, *et al.* An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry* 2005; **57:** 430–2.
4. Coric V, *et al.* Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. *Biol Psychiatry* 2005; **58:** 424–8.
5. Coric V, *et al.* Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with trichotillomania. *J Clin Psychiatry* 2007; **68:** 170–1.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Rilasat; Rilutek; ***Austral.:*** Rilutek; ***Austria:*** Rilutek; ***Belg.:*** Rilutek; ***Braz.:*** Rilutek; ***Canad.:*** Rilutek; ***Chile:*** Rilutek; ***Cz.:*** Rilutek; ***Denm.:*** Rilutek; ***Fin.:*** Rilutek; ***Fr.:*** Rilutek; ***Ger.:*** Rilutek; ***Hong Kong:*** Rilutek; ***Hung.:*** Rilutek; ***Irl.:*** Rilutek; ***Israel:*** Rilutek; ***Ital.:*** Rilutek; ***Jpn:*** Rilutek; ***Mex.:*** Rilutek; ***Neth.:*** Rilutek; ***Norw.:*** Rilutek; ***NZ:*** Rilutek; ***Pol.:*** Rilutek; ***Port.:*** Rilutek; ***S.Afr.:*** Rilutek; ***Singapore:*** Rilutek; ***Spain:*** Rilutek; ***Swed.:*** Rilutek; ***Switz.:*** Rilutek; ***Thai.:*** Rilutek; ***Turk.:*** Rilutek; ***UK:*** Rilutek; ***USA:*** Rilutek; ***Venez.:*** Rilutek.

Rimonabant *(USAN, rINN)*

Rimocaban; Rimonabantum; SR-141716. 5-(*p*-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinopyrazole-3-carboxamide.

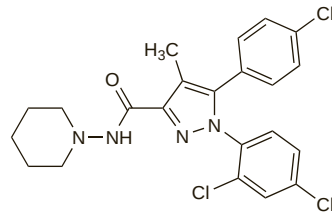
Римонабант

$C_{22}H_{21}Cl_3N_4O$ = 463.8.

CAS — 168273-06-1 (rimonabant); 158681-13-1 (rimonabant hydrochloride).

ATC — A08AX01.

ATC Vet — QA08AX01.



Profile

Rimonabant is a selective cannabinoid type-1 receptor antagonist used as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m^2), and also for overweight patients (BMI > 27 kg/m^2) who have associated risk factors such as type 2 diabetes mellitus or dyslipidaemia. It is given orally in doses of 20 mg daily before breakfast. However, following concern about psychiatric reactions marketing of rimonabant was suspended in Europe in October 2008.

Nausea, anxiety, and dizziness occur commonly with rimonabant. Depressive symptoms have also occurred and rimonabant should not be given to patients with major depression or to those being treated with antidepressants; it is also not recommended in patients with other uncontrolled serious psychiatric disorders. Since rimonabant is metabolised by the liver, caution is advised in patients with moderate hepatic impairment. Licensed product information does not recommend its use in patients with severe hepatic or renal impairment because of lack of data in these patient groups. Plasma concentrations of rimonabant are increased when given with ketoconazole; other CYP3A4 inhibitors might have the same effect.

Rimonabant is also being investigated as an aid for smoking cessation.

◊ The action and potential uses of rimonabant have been reviewed.[1-5] Rimonabant is a selective cannabinoid type-1 receptor antagonist that reduces the overactivity of the endocannabinoid (endogenous cannabinoid) system. Studies of rimonabant *in vitro* and in *animals* have shown that it inhibits the proliferation and maturation of adipocytes, improves lipid and glucose metabolism, and regulates food intake and energy balance.[1,3,4]

Four large multicentre randomised controlled studies have been carried out to examine the effects of rimonabant in obesity (RIO) in conjunction with a mildly hypocalorific diet (deficit of about 600 kcal/day),[6-9] and all studies showed that rimonabant was of benefit when given at a dose of 20 mg daily. A significant decrease in body-weight and waist circumference was reported from the RIO-Europe study[6] over 1 year, although results from the RIO-North America study[7] conducted over 2 years were more modest; both studies also showed improvement in cardiovascular risk factors. The RIO-Lipids study[8] examined the effects of rimonabant over 1 year in overweight or obese patients with untreated dyslipidaemias and noted improvement in several metabolic risk factors as well as weight loss. Similar results including improvement in plasma-glucose concentrations (as indicated by glycosylated haemoglobin measurements) were obtained in overweight or obese patients with type 2 diabetes mellitus given rimonabant over 1 year in the RIO-Diabetes study.[9] Meta-analysis[10] and systematic review[11] of the 4 studies in the RIO-programme agreed that rimonabant produced statistically greater weight loss than placebo, although some problems with methodology were noted. Since no follow-up data were reported, no conclusion could be reached about weight regain.[10] Of particular concern was the increase in incidence of psychiatric adverse effects such as depression and anxiety in the treatment group.[10]