Ketorolac is contra-indicated in patients with a history of hypersensitivity to aspirin or other NSAIDs, a history of asthma, nasal polyps, bronchospasm, or angioedema, a history of peptic ulceration or gastrointestinal bleeding, in patients with moderate or severe renal impairment, and in those with hypovolaemia or dehydration. Ketorolac should not be given to patients with coagulation or haemorrhagic disorders or those with confirmed or suspected cerebrovascular bleeding. It is contra-indicated as a prophylactic analgesic before surgery and for intraoperative use because of its inhibitory effects on platelets; it should also not be given postoperatively to those who have undergone procedures with a high risk of haemorrhage.

The total daily dose of ketorolac should be reduced in the elderly and in patients weighing less than 50 kg. It is recommended that patients with mild renal impairment should receive a reduced dose of ketorolac and undergo close monitoring of renal function. Ketorolac should be used with caution in heart failure, hepatic impairment and conditions leading to reduction in blood volume or in renal blood flow. Ketorolac should be withdrawn if clinical symptoms of hepatotoxicity develop.

Drowsiness and dizziness may affect the performance of skilled tasks such as driving.

Breast feeding. The concentration of ketorolac distributed into breast milk is very low and a study[1] considered that the amount ingested by the infant would probably be too small to be harmful. The American Academy of Pediatrics[2] also states that there have been no reports of any clinical effect on the infant associated with the use of ketorolac by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. However, the *BNF* and both UK and US licensed product information recommend that ketorolac should be avoided in mothers who are breast feeding.

1. Wischnik A, *et al.* The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. *Eur J Clin Pharmacol* 1989; **36:** 521–4.
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 07/11/07)

Interactions

For interactions associated with NSAIDs, see p.99.

Ketorolac should not be given to patients already receiving anticoagulants or to those who will require prophylactic anticoagulant therapy, including low-dose heparin. The risk of ketorolac-associated bleeding is also increased by other NSAIDs or aspirin and by pentoxifylline and use together should be avoided. Probenecid increases the half-life and plasma concentrations of ketorolac and the two drugs should not be given together.

Parasympathomimetics. Licensed product information for acetylcholine chloride ophthalmic preparations states that there have been reports that *acetylcholine* and *carbachol* have been ineffective when used in patients treated with topical (ophthalmic) NSAIDs.

Pharmacokinetics

Ketorolac trometamol is absorbed after intramuscular or oral doses. At physiological pH ketorolac trometamol dissociates to form an anionic ketorolac molecule which is less hydrophilic than the trometamol salt. The peak plasma concentration of ketorolac is reached within about 30 to 60 minutes; absorption after intramuscular injection may be slower than that after oral doses in some individuals. Ketorolac is over 99% bound to plasma proteins. It does not readily penetrate the blood-brain barrier. Ketorolac crosses the placenta and small amounts of drug are distributed into breast milk. The terminal plasma half-life is about 4 to 6 hours, but is about 6 to 7 hours in the elderly and 9 to 10 hours in patients with renal dysfunction. The major metabolic pathway is glucuronic acid conjugation; there is some *para*-hydroxylation. About 90% of a dose is excreted in urine as unchanged drug and conjugated and hydroxylated metabolites, the remainder is excreted in the faeces.

◊ References.

1. Kauffman RE, *et al.* Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children. *Clin Pharmacol Ther* 1999; **65:** 382–8.
2. Hamunen K, *et al.* Stereoselective pharmacokinetics of ketorolac in children, adolescents and adults. *Acta Anaesthesiol Scand* 1999; **43:** 1041–6.
3. Dsida RM, *et al.* Age-stratified pharmacokinetics of ketorolac tromethamine in pediatric surgical patients. *Anesth Analg* 2002; **94:** 266–70.
4. McAleer SD, *et al.* Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *J Clin Pharmacol* 2007; **47:** 13–18.

Uses and Administration

Ketorolac, a pyrrolizine carboxylic acid derivative structurally related to indometacin (p.66), is an NSAID (p.99). It is used principally as an analgesic.

Ketorolac is used intramuscularly, intravenously, or orally as the trometamol salt in the short-term management of moderate to severe **postoperative pain**. However, it should be noted that because of concerns over the high incidence of reported adverse effects with ketorolac its dosage and maximum duration of use are restricted. The recommended maximum duration for parenteral therapy is 2 days in the UK, and patients should be transferred to oral therapy as soon as possible; oral use is limited to 7 days. In the USA it is recommended that the maximum combined duration of use of parenteral and oral ketorolac should not exceed 5 days.

- In the UK the recommended initial dose by the *parenteral* route is 10 mg of ketorolac trometamol followed by 10 to 30 mg every 4 to 6 hours as required, although ketorolac may be given as often as every 2 hours in the initial postoperative period if required. The total maximum daily dose is 90 mg (60 mg in the elderly, patients with mild renal impairment, and in those weighing less than 50 kg). Intravenous injections should be given over at least 15 seconds. During transfer from parenteral to oral therapy the combined daily dose for all forms of ketorolac trometamol should not exceed 90 mg (60 mg in the elderly, patients with mild renal impairment, and in those weighing less than 50 kg) of which no more than 40 mg should be given orally.
- Regimens in use in the USA include a single intramuscular dose of 60 mg or a single intravenous dose of 30 mg, or a multiple-dose regimen comprising 30 mg every 6 hours intramuscularly or intravenously, up to a maximum of 120 mg daily. These doses should be halved in the elderly, those with renal impairment, and those weighing less than 50 kg.
- The recommended *oral* dose in the UK is 10 mg every 4 to 6 hours (every 6 to 8 hours in the elderly) to a maximum of 40 mg daily for a maximum duration of 7 days.
- In the USA the recommended oral dose is 20 mg (10 mg in the elderly, the renally impaired, and those weighing under 50 kg), followed by 10 mg every 4 to 6 hours to a maximum of 40 mg daily.

For doses in children see Administration in Children, below.

Ketorolac trometamol is used as 0.5% eye drops to relieve **ocular itching** associated with seasonal allergic conjunctivitis. Ketorolac trometamol eye drops 0.5% have also been used for the topical treatment of **cystoid macular oedema** and for the prevention and reduction of **inflammation** associated with ocular surgery. In the USA, a 0.4% eye drop is also available for postoperative ocular inflammation.

◊ Reviews.

1. Gillis JC, Brogden RN. Ketorolac: a reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; **53:** 139–88.

Administration in children. In the USA, children aged between 2 to 16 years may be given a single intramuscular dose of 1 mg/kg of ketorolac trometamol up to a maximum of 30 mg or a single intravenous dose of 0.5 mg/kg up to a maximum of 15 mg. In the UK, parenteral ketorolac is only recommended for those aged 16 and over; doses are as for adults (see above).

Oral ketorolac is not licensed for use in children.

Administration in renal impairment. Ketorolac is contra-indicated in patients with moderate to severe renal impairment; for suggested doses in less advanced renal impairment, see Uses and Administration, above.

Preparations

USP 31: Ketorolac Tromethamine Injection; Ketorolac Tromethamine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Acular; Dolten; Kelac; Kemanat; Kerarer; Ketopharm; Klenac; Nolarac†; Poenkerat; Sinalgico; Teledol; Tenkdol; Unicalm; ***Austral.:*** Acular; Toradol; ***Austria:*** Acular; ***Belg.:*** Aculare; Taradyl; ***Braz.:*** Acular; Cetrolac; Deocil†; Toradol; Toragesic; ***Canad.:*** Acular; Toradol; ***Chile:*** Acular; Brodifac; Burten; Dilox; Dolgenal; Findedol†; Netaf; Poenkerat; Syndol; ***Denm.:*** Acular; Toradol; ***Fin.:*** Acular; Toradol; ***Fr.:*** Acular; ***Ger.:*** Acular; ***Gr.:*** Acular; ***Hong Kong:*** Acular; Keto; Toradol; ***India:*** Cadolac; Ketanov; Ketlur; Ketodrops; Ketonic†; Torolac; ***Indon.:*** Dolac; Ketopain; Lantipain; Remopain; Rolac; Scelto; Toradol; Toramine; Torasic; Torpain; Trolac; Xevolac; ***Irl.:*** Acular; ***Israel:*** Topadol; ***Ital.:*** Acular; Lixidol; Tora-Dol; ***Malaysia:*** Acular; Ketanov†; Keto; Toradol; ***Mex.:*** Acularen; Ainelac; Aitornet; Alidol; Apotoke; Brunacol; Celfax; Doket; Dolac; Dolcoplaz; Dolikan; Dolotor†; Drometak; Efimerol; Estopein; Exorol; Findol†; Finlac; Geldako; Glicima; Godek; Italker; Kendolit; Koprak; Lacdol; Lacomin; Lenaken; Lorotec; Mavidol; Onemer; Plusindol; Rapix; Rolesen; Rolodiquim; Rometran-K; Sebapain; Supradol; Toloran; Toral; Torkol; Trodorol; Tromedal; Ultilap; Zafidol; ***Neth.:*** Acular; ***Norw.:*** Toradol; ***NZ:*** Acular; ***Philipp.:*** Acular; Ketanov; Ketomed; Kortezor; Toradol; ***Port.:*** Acular; Elipa; Toradol; ***Rus.:*** Adolor (Адолор); Dolac (Долак); Ketalgin (Кеталгин); Ketanov (Кетанов); Ketorol (Кеторол); ***S.Afr.:*** Acular; Tora-Dol; ***Singapore:*** Acular; Keto†; Toradol†; ***Spain:*** Acular; Algikey; Droal; Tonum; Toradol; ***Swed.:*** Toradol; ***Switz.:*** Acular; Tora-Dol; ***Thai.:*** Acular; ***Turk.:*** Acular; ***UK:*** Acular; Toradol; ***USA:*** Acular; Toradol†; ***Venez.:*** Acular†; Dolak; Kelac; Ketorel†; Ketorol†; Notolac; Ocudol; Poenkerat.

Multi-ingredient: ***Mex.:*** Gammadol; Sinergix.

Leflunomide *(BAN, USAN, rINN)*

HWA-486; Leflunomid; Leflunomida; Léflunomide; Leflunomidi; Leflunomidum; RS-34821; SU-101. α,α,α-Trifluoro-5-methyl-4-isoxazolecarboxy-*p*-toluidide.

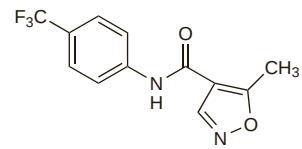
Лефлуномид

$C_{12}H_9F_3N_2O_2$ = 270.2.

CAS — 75706-12-6.

ATC — L04AA13.

ATC Vet — QL04AA13.



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

Ph. Eur. 6.2 (Leflunomide). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; freely soluble in methyl alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 31 (Leflunomide). White to almost white powder. Practically insoluble in water; freely soluble in acetone, in acetonitrile, in alcohol, in chloroform, in ethyl acetate, in isopropyl alcohol, and in methyl alcohol. Store at a temperature not exceeding 30°.

Adverse Effects, Treatment and Precautions

Common adverse effects seen with leflunomide are hypertension, gastrointestinal disturbances (particularly diarrhoea), weight loss, headache, dizziness, leucopenia, asthenia, paraesthesia, joint disorders and synovitis, upper respiratory-tract infections, alopecia, eczema, and dry skin. Hypersensitivity reactions may occur and a few cases of Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, or vasculitis have been reported. Hepatotoxicity has occurred. It is usually mild and reversible but rare cases of severe, sometimes fatal, liver disease, including acute hepatic necrosis, have been seen particularly in the first 6 months of therapy. Other adverse effects that have been reported include anxiety, peripheral neuropathy, hypokalaemia, and mild hyperlipidaemia. There have been rare reports of pancytopenia, agranulocytosis, and thrombocytopenia; these effects are more common when leflunomide is given with other myelosuppressive drugs (see Interactions, below). There have been occasional reports of pancreatitis, interstitial lung disease, and severe infections, including fatal sepsis. Renal failure has also been reported.

The active metabolite of leflunomide, A-771726, has a half-life of about 2 weeks. Consequently, the adverse effects of leflunomide may continue even after therapy has been stopped. When severe reactions occur, a drug washout procedure (see below) may be required.

Leflunomide should not be given to immunocompromised patients or to patients with severe infections, hepatic or moderate to severe renal impairment, severe hypoproteinaemia, or bone-marrow dysplasia. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection. Intra-uterine devices should be used with caution during immunosuppressive treatment as there is an increased risk of infection. Live vaccines should be avoided for the same reason. Blood pressure should be monitored regularly during therapy.

In the UK, liver enzyme values should be checked before beginning therapy and at fortnightly intervals during the first 6 months of treatment; US licensed product information recommends monthly monitoring for the first 6 months. Subsequent monitoring should be carried out at 6- to 8-week intervals. Dosage should be reduced if moderate elevations of liver enzyme values occur (see Administration in Hepatic Impairment, below); for persistent or more severe elevations leflunomide should be stopped and washout procedures begun. Monitoring of liver enzymes should be continued after stopping therapy until they return to within the normal range. Blood counts should also be checked at the same time as liver enzyme values.

Effects on the lungs. Up to December 2006, the Australian Adverse Drug Reactions Advisory Committee had received 142 reports of respiratory symptoms with leflunomide use since its introduction in 2000.[1] Of these, 22 reports mentioned at least one of the following serious reactions: pneumonitis (8), interstitial lung disease (9), lung infiltration (4), or pulmonary fibrosis (3); it was considered that all these were likely to represent interstitial lung disease. Four patients died, but relative causality was difficult to assign as methotrexate was also given in many cases, however, several patients had been on methotrexate long-term without any problems. It was recommended that the pulmonary status of patients should be considered before starting leflunomide and monitored during treatment; if symptoms such as cough or dyspnoea develop or worsen, leflunomide may need to be stopped.

The risk of interstitial lung disease with leflunomide has also been assessed using data from a large cohort study.[2] This study found that, overall, there was a twofold increase in the risk of interstitial lung disease in patients treated with leflunomide compared with those who did not receive leflunomide. However, subgroup analysis showed that this increase was limited to those patients with a history of methotrexate use or interstitial lung disease; in those with no previous methotrexate use or no history of interstitial lung disease, there was no increased risk with leflunomide. See also under Interactions, below.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and interstitial lung disease. *Aust Adverse Drug React Bull* 2006; **25:** 22–3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0612.pdf (accessed 13/06/08)
2. Suissa S, *et al.* Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum* 2006; **54:** 1435–9.

Effects on the nervous system. Peripheral neuropathy has been associated with leflunomide use.[1-3] Up to October 2006, the Australian Adverse Drug Reactions Advisory Committee had received 659 reports of adverse reactions associated with leflunomide, 30 of which mentioned neuropathy or peripheral neuropathy;[4] leflunomide was the sole suspected drug in 24 of these cases. Recovery was noted after drug withdrawal in 6 patients, of whom 3 underwent washout procedures; however, 15 patients had not recovered at the time of the reports and there was no information on the remaining cases.

1. Bonnel RA, Graham DJ. Peripheral neuropathy in patients treated with leflunomide. *Clin Pharmacol Ther* 2004; **75:** 580–5.
2. Martin K, *et al.* Neuropathy associated with leflunomide: a case series. *Ann Rheum Dis* 2005; **64:** 649–50.
3. Metzler C, *et al.* Peripheral neuropathy in patients with systemic rheumatic diseases treated with leflunomide. *Ann Rheum Dis* 2005; **64:** 1798–1800.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Leflunomide and peripheral neuropathy. *Aust Adverse Drug React Bull* 2006; **25:** 18–19. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 13/06/08)

Effects on the skin. A 58-year-old woman developed lupus erythematosus 1 month after starting leflunomide 20 mg daily for treatment of Sjögren's syndrome.[1] The rash resolved within 4 weeks of stopping leflunomide but recurred on 2 separate occasions when she took the drug again.

1. Gensburger D, *et al.* Lupus erythematosus with leflunomide: induction or reactivation? *Ann Rheum Dis* 2005; **64:** 153–5.

Overdose. Unintentional overdoses with leflunomide have been reported in 2 patients. In one case, no adverse effects were seen in a 40-year-old woman who had mistakenly taken both a 100-mg and a 20-mg tablet daily for 28 days;[1] in another case, a 70-year-old man who took 100 mg weekly, in addition to 20 mg daily, for over 2 years was found to have interstitial nephritis which improved after leflunomide was stopped.[2] In both cases, the 100-mg dose was meant to be taken for 2 or 3 days only as a loading dose.

1. Kamali S, *et al.* An unusual overdose of leflunomide in a patient with rheumatoid arthritis. *Ann Pharmacother* 2004; **38:** 1320–1.
2. Haydar AA, *et al.* Chronic overdose of leflunomide inducing interstitial nephritis. *Nephrol Dial Transplant* 2004; **19:** 1334–5.

Pregnancy. Leflunomide is contra-indicated during pregnancy as its active metabolite has been shown to be teratogenic in *animals.* Pregnancy should therefore be excluded before beginning therapy, and licensed product information states that reliable contraception should be used in women of child-bearing potential (UK product information also recommends reliable contraception in men treated with leflunomide). Women wishing to become pregnant should wait for 2 years after stopping therapy, or if this is infeasible, a washout procedure (see below) should be performed and a waiting period of 6 weeks be observed from the time plasma concentrations of the metabolite fall below 20 nanograms/mL before attempting conception. A washout procedure with a waiting period of at least 3 months is recommended in men who wish to father children. Women who become pregnant during therapy should also undergo a washout procedure.

Washout procedure. If serious adverse effects occur during leflunomide therapy, licensed product information recommends that a drug washout procedure is performed. This may also be considered if a patient becomes pregnant while taking leflunomide, or if it is necessary to swap to another disease-modifying antirheumatic drug such as methotrexate.

For the washout procedure, either 8 g of colestyramine is given orally 3 times daily or 50 g of activated charcoal is given orally or via a nasogastric tube 4 times daily. Therapy is normally continued for 11 days, but should be repeated until plasma concentrations of the primary metabolite A-771726 are below 20 nanograms/mL, verified by two separate tests at least 14 days apart.

Interactions

Increased adverse effects may occur if leflunomide is given with other hepatotoxic or myelosuppressive drugs; these effects may also be seen when leflunomide treatment is followed by such drugs without a drug washout procedure (above). The risks of combined use with other disease-modifying antirheumatic drugs, particularly in the long term, have not been studied and such use is not advised in the UK; however, US licensed product information recommends that if long-term combined use is necessary, liver enzyme values and blood counts should be monitored monthly rather than every 6 to 8 weeks (see Adverse Effects, Treatment, and Precautions, above).

See above for precautions about use with live vaccines.

Anticoagulants. For reference to the effect of leflunomide on the activity of *warfarin*, see under Immunosuppressants, p.1431.

Methotrexate. Leflunomide therapy has been rarely associated with pancytopenia. Of the 18 cases (median age 65.5 years) reported in one series, 14 patients were also receiving methotrexate therapy.[1] The pancytopenia was typically severe and required hospitalisation; 5 patients had died, 4 of whom were also taking methotrexate. Time to onset of pancytopenia ranged from 11 days to 4 years. The authors concluded that the risk of pancytopenia during leflunomide treatment appeared to increase when used with methotrexate, and emphasised the importance of ongoing monitoring of blood counts.

Leflunomide therapy has also been rarely associated with interstitial lung disease including interstitial pneumonitis (see above). Up to March 2006, the Centre for Adverse Reactions Monitoring (CARM) in New Zealand[2] had received 7 reports of pneumonitis associated with leflunomide in patients who were also taking methotrexate. Of these, 4 had taken methotrexate (which is also associated with pneumonitis) for more than 1 year. Respiratory symptoms developed 12 to 36 weeks after starting leflunomide therapy; 5 patients recovered, 1 died, and another improved but had some persisting respiratory impairment.

For advice on a drug washout procedure, see above.

1. Chan J, *et al.* Leflunomide-associated pancytopenia with or without methotrexate. *Ann Pharmacother* 2004; **38:** 1206–11.
2. Savage R. Leflunomide and pneumonitis. *Prescriber Update* 2006; **27:** 7–9.

Pharmacokinetics

After oral doses leflunomide undergoes first-pass metabolism in the liver and gut wall to A-771726 (teriflunomide), which is responsible for the majority of the *in vivo* activity. The bioavailability of leflunomide after oral doses ranges from 82 to 95%. Peak plasma concentrations of the active metabolite may occur from 1 to 24 hours after a dose.

A-771726 is more than 99% bound to plasma proteins, mainly albumin. It is some further metabolism. About 43% of a dose is eliminated in the urine, mainly as glucuronides, and 48% is eliminated in the faeces via the bile.

A-771726 has an elimination half-life of about 2 weeks, which is thought to be mainly due to enterohepatic recycling. Colestyramine or activated charcoal are able to interrupt recycling and can therefore accelerate drug elimination.

Studies in *animals* suggest that leflunomide or its metabolites are distributed into breast milk.

◊ References.

1. Rozman B. Clinical pharmacokinetics of leflunomide. *Clin Pharmacokinet* 2002; **41:** 421–30.
2. Shi J, *et al.* Population pharmacokinetics of the active metabolite of leflunomide in pediatric subjects with polyarticular course juvenile rheumatoid arthritis. *J Pharmacokinet Pharmacodyn* 2005; **32:** 419–39.
3. Chan V, *et al.* Population pharmacokinetics and association between A77 1726 plasma concentrations and disease activity measures following administration of leflunomide to people with rheumatoid arthritis. *Br J Clin Pharmacol* 2005; **60:** 257–64.

Uses and Administration

Leflunomide has immunosuppressant and antiproliferative properties. It is used as a disease-modifying antirheumatic drug in the treatment of active rheumatoid arthritis. It is also used in the treatment of active psoriatic arthritis and has been investigated in the management of various solid neoplasms.

Because of the long half-life of the principal metabolite, a loading dose of leflunomide is required to reach steady-state concentrations relatively rapidly. Therapy should start with an oral loading dose of 100 mg once daily for 3 days. However, in practice, the loading dose may be omitted in those patients at an increased risk of adverse effects, particularly haematological or hepatic effects. The maintenance dose is 10 to 20 mg once daily for rheumatoid arthritis and 20 mg once daily for psoriatic arthritis. Dose adjustments may be necessary in patients who develop abnormal liver enzyme values, see below. The therapeutic effect usually starts after 4 to 6 weeks of therapy and further improvements may occur for up to 6 months.

Administration in hepatic impairment. Leflunomide is contra-indicated in patients with hepatic impairment. Patients who develop moderate elevations of liver enzyme values (defined as transaminase levels 2 to 3 times the normal upper limit) while receiving leflunomide treatment should have their dose reduced to 10 mg daily; if necessary, monitoring of liver enzyme values should also be performed at weekly intervals. If moderate elevations persist or if severe elevations occur, leflunomide should be stopped and washout procedures started (see above).

Inflammatory bowel disease. Leflunomide has been tried, with some success, in the management of Crohn's disease (p.1697).

References.

1. Prajapati DN, *et al.* Leflunomide treatment of Crohn's disease patients intolerant to standard immunomodulator therapy. *J Clin Gastroenterol* 2003; **37:** 125–8.

Rheumatoid arthritis. References to the use of leflunomide in rheumatoid arthritis (p.11).

1. Strand V, *et al.* Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999; **159:** 2542–50.
2. Prakash A, Jarvis B. Leflunomide: a review of its use in active rheumatoid arthritis. *Drugs* 1999; **58:** 1137–64.
3. Emery P, *et al.* A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000; **39:** 655–65.
4. McCarey DW, *et al.* Leflunomide in treatment of rheumatoid arthritis. *Lancet* 2002; **359:** 1158.
5. Miceli-Richard C, Dougados M. Leflunomide for the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2003; **4:** 987–97.

6. Maddison P, *et al.* Leflunomide in rheumatoid arthritis: recommendations through a process of consensus. *Rheumatology (Oxford)* 2005; **44:** 280–6. Correction. *ibid.*; 569.
7. Silverman E, *et al.* Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2005; **52:** 554–62.
8. Silverman E, *et al.* Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med* 2005; **352:** 1655–66.

Spondyloarthropathies. References to the use of leflunomide in ankylosing spondylitis and psoriatic arthritis (see Spondyloarthropathies, p.13).

1. Cuchacovich M, Soto L. Leflunomide decreases joint erosions and induces reparative changes in a patient with psoriatic arthritis. *Ann Rheum Dis* 2002; **61:** 942–3.
2. Kaltwasser JP, *et al.* Treatment of Psoriatic Arthritis Study Group. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004; **50:** 1939–50.
3. Haibel H, *et al.* Six months open label trial of leflunomide in active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 124–6.
4. van Denderen JC, *et al.* Double blind, randomised, placebo controlled study of leflunomide in the treatment of active ankylosing spondylitis. *Ann Rheum Dis* 2005; **64:** 1761–4.
5. Schmitt J, Wozel G. Psoriasis-arthritis—Langzeit-therapie zweier Patienten mit Leflunomid. *J Dtsch Dermatol Ges* 2005; **2:** 763–6.
6. Nash P, *et al.* Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. *Dermatology* 2006; **212:** 238–49.

Preparations

USP 31: Leflunomide Tablets.

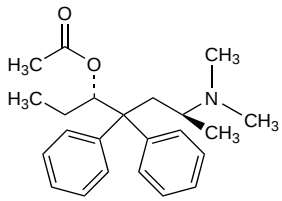
Proprietary Preparations (details are given in Part 3)
Arg.: Afiancen; Arava; Filartros; Inmunoartro; Lefluar; Molagar†; ***Austral.:*** Arabloc; Arava; ***Austria:*** Arava; ***Belg.:*** Arava; ***Braz.:*** Arava; ***Canad.:*** Arava; ***Chile:*** Arava; Artrimod; ***Cz.:*** Arava; ***Denm.:*** Arava; ***Fin.:*** Arava; ***Fr.:*** Arava; ***Ger.:*** Arava; ***Gr.:*** Arava; ***Hong Kong:*** Arava; ***Hung.:*** Arava; ***India:*** Arava; Lara†; Lefumide; Rumalef; ***Indon.:*** Arava; ***Irl.:*** Arava; ***Israel:*** Arava; ***Ital.:*** Arava; ***Malaysia:*** Arava; ***Mex.:*** Arava; ***Neth.:*** Arava; ***Norw.:*** Arava; ***NZ:*** Arava; ***Philipp.:*** Arava; ***Pol.:*** Arava; ***Port.:*** Arava; ***Rus.:*** Arava (Арава); ***S.Afr.:*** Arava; ***Singapore:*** Arava; ***Spain:*** Arava; ***Swed.:*** Arava; ***Switz.:*** Arava; ***Thai.:*** Arava; ***Turk.:*** Arava; ***UK:*** Arava; ***USA:*** Arava; ***Venez.:*** Arava.

Levacetylmethadol *(rINN)*

l-α-Acetylmethadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); LAM; Levacetilmetadol; Levacetylmetadol; Lévacétylméthadol; Levacetylmethadolum; Levasetyylimetadoli; Levomethadyl Acetate *(USAN)*; *l*-Methadyl Acetate. (–)-4-Dimethylamino-1-ethyl-2,2-diphenylpentyl acetate.

Левацетилметадол

$C_{23}H_{31}NO_2$ = 353.5.
CAS — 1477-40-3 (levomethadyl); 34433-66-4 (levacetylmethadol).
ATC — N07BC03.
ATC Vet — QN07BC03.



Levacetylmethadol Hydrochloride *(rINNM)*

Hidrocloruro de levacetilmetadol; LAAM (levacetylmethadol or levacetylmethadol hydrochloride); Lévacétylméthadol, Chlorhydrate de; Levacetylmethadoli Hydrochloridum; Levomethadyl Acetate Hydrochloride *(USAN)*; MK-790. (–)-(3*S*,6*S*)-6-(Dimethylamino)-4,4-diphenyl-3-heptanol acetate hydrochloride.

Левацетилметадола Гидрохлорид

$C_{23}H_{31}NO_2$,HCl = 390.0.
CAS — 43033-72-3.
ATC — N07BC03.
ATC Vet — QN07BC03.

Profile

Levacetylmethadol, a diphenylheptane derivative, is a long-acting opioid analgesic (p.104); it is a derivative of methadone (p.84). It was used as the hydrochloride in the management of opioid dependence. However, the proarrhythmic effects led to its withdrawal in the EU and the USA.

Preparations

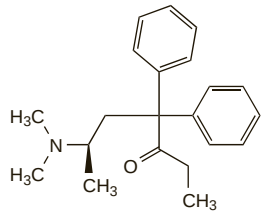
Proprietary Preparations (details are given in Part 3)
Irl.: OrLAAM†; ***Spain:*** OrLAAM†; ***USA:*** OrLAAM†.

Levomethadone Hydrochloride *(rINNM)* ⊗

Hidrocloruro de levometadona; Levometadonhidroklorid; Levometadonhydroklorid; Levometadonihydrokloridi; Levometadono hidrochloridas; Lévométhadone, chlorhydrate de; Levomethadon-hydrochlorid; Levomethadoni hydrochloridum; (–)-Methadone Hydrochloride. (–)-6-Dimethylamino-4,4-diphenylheptan-3-one hydrochloride.

Левометадона Гидрохлорид

$C_{21}H_{27}NO$,HCl = 345.9.
CAS — 125-58-6 (levomethadone); 5967-73-7 (levomethadone hydrochloride).



(levomethadone)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Levomethadone Hydrochloride). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. Protect from light.

Profile

Levomethadone is an opioid analgesic (p.101). It is the active isomer of racemic methadone (p.82) and is used similarly, as the hydrochloride, in the treatment of severe pain and in the management of opioid dependence.

Preparations

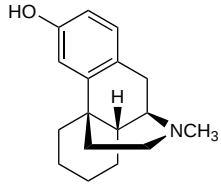
Proprietary Preparations (details are given in Part 3)
Ger.: L-Polamidon.

Levorphanol Tartrate *(BANM, rINNM)*

Levorphan Tartrate; Levorphanol Bitartrate; Lévorphanol, Tartrate de; Levorphanoli Tartras; Methorphinan Tartrate; Tartrato de levorfanol. (–)-9a-Methylmorphinan-3-ol hydrogen tartrate dihydrate.

Леворфанола Тартрат

$C_{17}H_{23}NO,C_4H_6O_6,2H_2O$ = 443.5.
CAS — 77-07-6 (levorphanol); 125-72-4 (anhydrous levorphanol tartrate); 5985-38-6 (levorphanol tartrate dihydrate).



(levorphanol)

Pharmacopoeias. In *US*.
USP 31 (Levorphanol Tartrate). A practically white, odourless, crystalline powder. Soluble 1 in 50 of water and 1 in 120 of alcohol; insoluble in chloroform and in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Profile

Levorphanol tartrate, a phenanthrene derivative, is a potent opioid analgesic (p.101) used in the management of moderate to severe pain. The analgesic effect usually begins about 10 to 60 minutes after oral doses and lasts up to about 8 hours. A usual initial oral dose of levorphanol tartrate is 2 mg repeated in 6 to 8 hours if necessary; the dose may be increased to 3 mg every 6 to 8 hours, adjusted according to response. The maximum initial daily dose in non-opioid tolerant patients should not exceed 12 mg. Elderly or debilitated patients may require lower doses; initial doses should be reduced by 50% or more.

Levorphanol tartrate has also been given by intramuscular, subcutaneous, or slow intravenous injection for pain relief and for premedication.

Preparations

USP 31: Levorphanol Tartrate Injection; Levorphanol Tartrate Tablets.

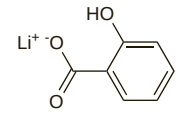
Proprietary Preparations (details are given in Part 3)
USA: Levo-Dromoran†.

Lithium Salicylate

Lithium Salicylicum; Salicilato de litio.

Лития Салицилат

$C_7H_5LiO_3$ = 144.1.
CAS — 552-38-5.



Profile

Lithium salicylate is a salicylic acid derivative (see Aspirin, p.20) that has been used in rheumatic disorders, but its use cannot be recommended because of the pharmacological effect of the lithium ion.

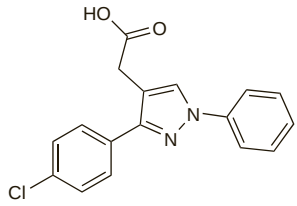
Lithium salicylate is used in homoeopathic medicine.

Lonazolac Calcium *(rINNM)*

Calcii Lonazolacum; Lonatsolaakkikalsium; Lonazolac Calcique; Lonazolaco cálcico; Lonazolacum Calcicum; Lonazolakkalcium. Calcium 3-(4-chlorophenyl)-1-phenylpyrazol-4-ylacetate.

Кальций Лоназолак

$C_{34}H_{24}CaCl_2N_4O_4$ = 663.6.
CAS — 53808-88-1 (lonazolac); 75821-71-5 (lonazolac calcium).
ATC — M01AB09.
ATC Vet — QM01AB09.



(lonazolac)

Profile

Lonazolac calcium is an NSAID (p.96). It has been given orally and rectally in the treatment of pain, inflammation, and musculoskeletal and joint disorders.

Preparations

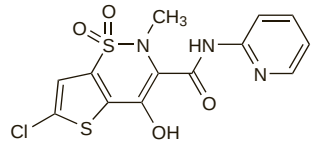
Proprietary Preparations (details are given in Part 3)
Austria: Irritren†; ***Ger.:*** Argun†; arthro akut†; ***Port.:*** Atrilon†.

Lornoxicam *(BAN, USAN, rINN)*

Chlorotenoxicam; Chlortenoxicam; CTX; Lornoksikaami; Lornoksikam; Lornoxicamum; Lornoxicanum; Lornoxikam; Ro-13-9297; TS-110. 6-Chloro-4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-thieno[2,3-e][1,2]-thiazine-3-carboxamide 1,1-dioxide.

Лорноксикам

$C_{13}H_{10}ClN_3O_4S_2$ = 371.8.
CAS — 70374-39-9.
ATC — M01AC05.
ATC Vet — QM01AC05.



Profile

Lornoxicam, an oxicam derivative, is an NSAID (p.96). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis; it is also used in the treatment of other painful conditions including postoperative pain.

In the treatment of osteoarthritis and rheumatoid arthritis lornoxicam is given in an initial oral daily dose of 12 mg in two or three divided doses; if necessary the daily dose may be increased to a maximum of 16 mg.

Lornoxicam is given in oral doses of 8 to 16 mg daily for the treatment of pain. Similar doses may be given by intravenous or