rheumatoid arthritis, and in peri-articular disorders such as bursitis and tendinitis. It is also used in dysmenorrhoea, postoperative pain, in painful and inflammatory conditions such as acute gout or soft-tissue disorders, and to reduce fever. Dexketoprofen is used in the treatment of mild to moderate pain such as musculoskeletal pain, dysmenorrhoea, or dental pain.

In the treatment of rheumatic disorders a usual oral daily dose of ***ketoprofen*** is 100 to 200 mg in 2 to 4 divided doses; modified-release formulations taken once daily may also be used. Some licensed product information suggests initial oral doses of 75 mg three times daily or 50 mg four times daily increased as needed to a maximum of 300 mg daily in divided doses. Ketoprofen may also be given rectally as suppositories in a dose of 100 mg at night or 100 mg twice daily. It is recommended that the total daily combined oral and rectal dose should not exceed 200 mg. The usual oral dose for the treatment of other painful conditions including dysmenorrhoea is 25 to 50 mg every 6 to 8 hours. For details on the use of ketoprofen in patients with hepatic or renal impairment, see below.

Ketoprofen may be given by deep intramuscular injection into the gluteal muscle for acute exacerbations of musculoskeletal, joint, peri-articular and soft-tissue disorders and in the management of pain after orthopaedic surgery. Doses of 50 to 100 mg may be given every 4 hours, up to a maximum dose of 200 mg in 24 hours for up to 3 days. In some countries, ketoprofen has also been given intravenously in similar doses.

Ketoprofen may be applied as a 2.5% gel for local pain relief. Doses vary slightly between preparations: typically, they are applied 2 to 4 times daily for up to 10 days.

Dexketoprofen is given orally as the trometamol salt. Doses are expressed in terms of the base; dexketoprofen trometamol 36.9 mg is equivalent to about 25 mg of dexketoprofen. Usual doses are 12.5 mg every 4 to 6 hours or 25 mg every 8 hours; the total daily dose should not exceed 75 mg. Elderly patients should be started on a total daily dose not exceeding 50 mg. Dose reductions are also necessary in patients with hepatic or renal impairment, see below. It is usually recommended that NSAIDs are taken with or after food to reduce any adverse gastrointestinal effects; however, licensed product information for dexketoprofen states that absorption is delayed if the drug is taken with food and therefore recommends that in acute pain dexketoprofen should be given at least 30 minutes before food.

Ketoprofen has also been used as the lysine and as the sodium salt.

◊ Reviews.

1. Mauleón D, *et al*. Preclinical and clinical development of dexketoprofen. *Drugs* 1996; **52:** 24–46.

Administration in hepatic or renal impairment. No specific dosage recommendations for racemic *ketoprofen* in patients with hepatic or renal impairment are given by UK licensed product information, although the drug is contra-indicated in severe renal impairment and it is advised that the dose be kept as low as possible and renal function be monitored in more moderate renal impairment (but see also Renal Impairment, above). In the USA, however, it has been recommended that patients with hepatic impairment and a serum albumin concentration of less than 3.5 g/dL should be given a maximum initial daily dose of 100 mg orally. Patients with mild renal impairment should be given a maximum daily dose of 150 mg and those with more severe impairment (GFR less than 25 mL/minute per 1.73 m^2 or end-stage renal impairment) should not exceed a maximum daily dose of 100 mg.

UK licensed product information for *dexketoprofen* recommends a reduced initial daily dose of 50 mg orally in patients with mild to moderate hepatic or mild renal impairment. Dexketoprofen should not be used in patients with severe hepatic or moderate to severe renal impairment.

Preparations

BP 2008: Ketoprofen Capsules; Ketoprofen Gel.

Proprietary Preparations (details are given in Part 3)
Arg.: Enantyum; Helenil; Orudis†; Profenid†; Salicrem K; ***Austral.:*** Orudis; Oruvail; ***Austria:*** Keprodol†; Profenid; Prontoket; ***Belg.:*** Bi-Rofenid; Fastum; Rofenid; ***Braz.:*** Artrifenil; Artrinid; Artrosil; Bi-Profenid; Ceprofen; Flamador; Ketop†; Profenid; ***Canad.:*** Apo-Keto; Novo-Keto; Orafen†; Orudis†; Rhodis; Rhovail†; ***Chile:*** Bonil; Cirus; Desketo; Dolo-Ketazon; Dolofar; Fastum; Flogofin; Profenid; Relatene; Talflex; ***Cz.:*** Bi-Profenid†; Dexoket; Fastum; Keplat; Ketesse; Ketobene†; Ketonal; Profenid; Prontoflex; Prontoket; Toprec†; ***Denm.:*** Orofen; Orudis; ***Fin.:*** Keto; Ketomex; Ketorin; Orudis; Zon; ***Fr.:*** Bi-Profenid; Ketum; Profenid; Topfena; Toprec; ***Ger.:*** Alrheumun; Effekton mit Ketoprofen; Gabrilen; Ketolist†; Orudis†; Phardol Schmerz; Spondylon; Sympal; Togal Mobil-Gel mit ketoprofen; ***Gr.:*** Drastirel; Farbovil; Ketodur†; Menaril; Nosatel; Oruvail; Profinject†; Totifen; Viaxal; ***Hong Kong:*** Fastum; Mohrus; Orudis; Oruvail; ***Hung.:*** Algoflex; Fastum; Ketodex; Ketospray; Profenid; Prontoket; ***India:*** Rofenid†; ***Indon.:*** Altofen; Fetik; Kaltrofen; Ketesse; Ketros; Lantiflam; Molaflam; Nasaflam; Nazovell; Ovurila; Profecom; Profenid; Profika; Pronalges; Protofen; Remapro; Rematof; Rhetoflam; Suprafenid; ***Irl.:*** Fastum; Keral; Orudis†; Orugesic; Oruvail; ***Israel:*** Ketonal†; Oruvail; Profenid; ***Ital.:*** Alket; Artrosilene; Desketo; Dolgosin; Enantyum; Euketos; Fastum; Flexen; Ibifen; Isofenal; Keplat; Ketartrium; Ketesse; Ketodol; Ketofarm; Ketoplus; Ketoselect; Lasonil CM; Meprofen; Oki; Orudis; Reuprofen; Toprek; Zepelindue†; ***Jpn:*** Mohrus; ***Malaysia:*** Apo-Keto; Fastum; Kenhancer; Ketotop†; Orudis; Oruvail†; Provail†; ***Mex.:*** Arket; Arthril; Bibix; Efiken; K-Profen; Kedunl†; Ketoflex; Orudis; Painsik; Profenid; Stadium; ***Neth.:*** Enantyum; Orudis; Oruvail; Oscorel; Rilies; Stadium; ***Norw.:*** Orudis; Zon; ***NZ:*** Orudis; Oruvail; ***Philipp.:*** Ketotop; Orudis; Udzapen; ***Pol.:*** Bi-Profenid; Dexak; Fastum; Febrofen; Ketonal; Ketoprom; Ketoproni!; Ketores; Ketospray; Profenid; Ultrafastin; ***Port.:*** Artrofene†; Deflogix†; Enantyum; Fastum; Keplat; Ketesse; Ketofene†; Profenid; Quetral; ***Rus.:*** Artrosilen (Артрозилен); Bystrumgel (Быструмгель); Dexalgin 25 (Дексалгин 25); Fastum (Фастум); Febrofid (Феброфид); Flexen (Флексен); Ketonal (Кетонал); Oki (Оки); ***S.Afr.:*** Fastum; Ketoflam; Myproflam; Orucote†; Oruject†; Oruvail; ***Singapore:*** Apo-Keto; Fastum; Kefentech; Kenhancer; Ketotop†; Oruvail; Provail†; ***Spain:*** Adolquir; Arcental; Badyket†; Enangel; Enantyum; Extraplus; Fastum; Ketesgel; Ketesse; Ketosolan; Orudis; Pyrsal; Quiralam; Quirgel; ***Swed.:*** Orudis; Prodon; Siduro; Zon; ***Switz.:*** Fastum; Ketesse; ***Thai.:*** Fastum; Kaprofen; Lolita; Oruvail; Profenid; Rofepain; Vestam; ***Turk.:*** Fastjel; Keto; Ketofen; Profenid; ***UK:*** Keral; Ketocid; Ketovail; Ketozip†; Larafen; Orudis; Oruvail; Powergel; Tiloket; ***USA:*** Orudis†; Oruvail†; ***Venez.:*** Dolomax; Kelfen; Keto; Keydol; Lindilan; Orofeno; Peindol; Profenid; Profenol†.

Multi-ingredient: ***Gr.:*** Profenil†; ***Mex.:*** Bifebral; Reumophan.

Ketorolac Trometamol *(BANM, rINNM)*

Ketorolaakkitrometamoli; Kétorolac trométamol; Ketorolac Tromethamine *(USAN)*; Ketorolaco trometamol; Ketorolacum Trometamoli; Ketorolacum trometamolum; Ketorolak Trometamol; Ketorolak z trometamolem; Ketorolaktrometamol; Ketorolak-trometamol; RS-37619-00-31-3. (±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1 : 1).

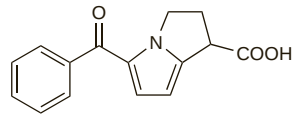
Кеторолак Трометамол

$C_{19}H_{24}N_2O_6$ = 376.4.

CAS — 74103-06-3 (ketorolac); 74103-07-4 (ketorolac trometamol).

ATC — M01AB15; S01BC05.

ATC Vet — QM01AB15; QS01BC05.



(ketorolac)

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

Ph. Eur. 6.2 (Ketorolac Trometamol). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 5.7 to 6.7. Protect from light.

USP 31 (Ketorolac Tromethamine). A white to off-white, crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol, in dehydrated alcohol, and in tetrahydrofuran; practically insoluble in acetone, in acetonitrile, in butyl alcohol, in dichloromethane, in dioxan, in ethyl acetate, in hexane, and in toluene. pH of a 1% solution in water is between 5.7 and 6.7. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

Concern over the high incidence of reported adverse effects with ketorolac trometamol has led to its withdrawal in some countries while in others its permitted dosage and maximum duration of treatment have been reduced.

Adverse effects reported include gastrointestinal disturbances including gastrointestinal bleeding (especially in the elderly), perforation, and peptic ulceration. Hypersensitivity reactions such as anaphylaxis, rash, bronchospasm, laryngeal oedema, and hypotension have also occurred. Other adverse effects reported include drowsiness, dizziness, headache, mental and sensory changes, psychotic reactions, sweating, dry mouth, thirst, fever, convulsions, myalgia, aseptic meningitis, hypertension, dyspnoea, pulmonary oedema, bradycardia, chest pain, palpitations, fluid retention, increases in blood urea and creatinine, acute renal failure, oedema, hyponatraemia, hyperkalaemia, urinary frequency or retention, nephrotic syndrome, flank pain with or without haematuria, purpura, thrombocytopenia, epistaxis, inhibition of platelet aggregation, increased bleeding time, postoperative wound haemorrhage, haematoma, flushing or pallor, and pancreatitis. Severe skin reactions including Stevens-Johnson syndrome and Lyell's syndrome have been reported. Liver function changes may occur; hepatitis and liver failure have been reported. There may be pain at the site of injection.

Ketorolac eye drops may produce transient stinging and other minor symptoms of ocular irritation. As with some other NSAIDs used in the eye, ketorolac has been implicated in reports of corneal toxicity (see p.45).

Incidence of adverse effects. Adverse effects reported with ketorolac are mainly those common to all NSAIDs with gastrointestinal reactions being the most frequent followed by haematological, renal, hypersensitivity, and then neurological reactions. From 1990 to 1993, 97 reactions with a fatal outcome were reported worldwide.[1] The causes of death were: gastrointestinal bleeding or perforation (47 cases); renal impairment or insufficiency (20); anaphylaxis or asthma (7); haemorrhagic reactions (4); and unexplained or miscellaneous causes (19). Concern over the safety of ketorolac has led to adverse reactions being monitored closely and to the implementation of restrictions on dose and duration of treatment (see Uses and Administration, below). A postmarketing surveillance study[2] examined the risks of parenteral ketorolac in 9 900 patients given 10 272 courses of ketorolac. The results indicated a dose-response relationship with average daily ketorolac dose for both gastrointestinal bleeding and operative site bleeding, the expected major risks, and an association between gastrointestinal bleeding and therapy for over 5 days. The risk of serious gastrointestinal bleeding and operative site bleeding was higher for elderly patients [licensed product information recommends that the elderly should not receive daily parenteral doses greater than 60 mg]. Although the overall associations between ketorolac use and both gastrointestinal bleeding and operative site bleeding are small, the risk becomes clinically important as doses increase, in elderly patients, and, for gastrointestinal bleeding only, when used for longer than 5 days.

US product information has consequently emphasised that ketorolac is a potent NSAID and is indicated only for the short-term management of moderate to severe pain and not for minor or chronic painful conditions; its use carries many risks and related adverse effects can be serious especially when used inappropriately. After examining data from the above study the EU Committee for Proprietary Medicinal Products adopted the opinion that ketorolac had a narrow therapeutic margin but that it was indicated for the short-term management of moderate to severe acute postoperative pain.

Further references to ketorolac's adverse effects are given below.[3-12]

1. CSM/MCA. Ketorolac: new restrictions on dose and duration of treatment. *Current Problems* 1993; **19:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 07/11/07)
2. Strom BL, *et al*. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: a postmarketing surveillance study. *JAMA* 1996; **275:** 376–82.
3. Rotenberg FA, Giannini VS. Hyperkalemia associated with ketorolac. *Ann Pharmacother* 1992; **26:** 778–9.
4. Boras-Uber LA, Brackett NC. Ketorolac-induced acute renal failure. *Am J Med* 1992; **92:** 450–2. Correction *ibid.*; **93:** 117.
5. Schoch PH, *et al*. Acute renal failure in an elderly woman following intramuscular ketorolac administration. *Ann Pharmacother* 1992; **26:** 1233–6.
6. Goetz CM, *et al*. Anaphylactoid reaction following ketorolac tromethamine administration. *Ann Pharmacother* 1992; **26:** 1237–8.
7. Randi ML, *et al*. Haemolytic uraemic syndrome during treatment with ketorolac trometamol. *BMJ* 1993; **306:** 186.
8. Fong J, Gora ML. Reversible renal insufficiency following ketorolac therapy. *Ann Pharmacother* 1993; **27:** 510–12.
9. Corelli RL, Gericke KR. Renal insufficiency associated with intramuscular administration of ketorolac tromethamine. *Ann Pharmacother* 1993; **27:** 1055–7.
10. Buck ML, Norwood VF. Ketorolac-induced acute renal failure in a previously healthy adolescent. *Pediatrics* 1996; **98:** 294–6.
11. Feldman HI, *et al*. Parenteral ketorolac: the risk for acute renal failure. *Ann Intern Med* 1997; **126:** 193–9.
12. Reinhart DJ, *et al*. Minimising the adverse effects of ketorolac. *Drug Safety* 2000; **22:** 487–97.

Precautions

As for NSAIDs in general, p.98.

In light of the concern over the toxicity of ketorolac it has been recommended that it should not be used during pregnancy or labour and some recommend that it should not be given to mothers who are breast feeding (but see below).

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.

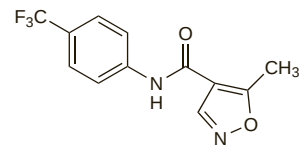
Лефлуномид

$C_{12}H_9F_3N_2O_2$ = 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.