Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ketazon†; ***Cz.:*** Ketazon†.
Multi-ingredient: ***Austria:*** Rheumesser; ***Cz.:*** Ketazon Compositum†.

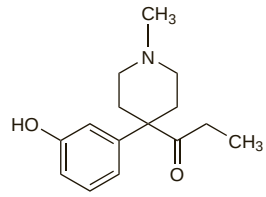
Ketobemidone Hydrochloride *(BANM, rINNM)*

Cétobémidone, chlorhydrate de; Cetobemidone Hydrochloride; Cetobemidoni hydrochloridum; Hidrocloruro de cetobemidona; Ketobemidon-hydrochlorid; Ketobemidonhydroklorid; Ketobemidoni Hydrochloridum; Ketobemidonihydrokloridi; Ketobemidono hidrochloridas. 1-(4-*m*-Hydroxyphenyl-1-methyl-4-piperidyl)propan-1-one hydrochloride.

Кетобемидона Гидрохлорид

$C_{15}H_{21}NO_2$,HCl = 283.8.

CAS — 469-79-4 (ketobemidone); 5965-49-1 (ketobemidone hydrochloride).
ATC — N02AB01.
ATC Vet — QN02AB01.



(ketobemidone)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Ketobemidone Hydrochloride). White or almost white, crystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 5.5.

Profile

Ketobemidone is an opioid analgesic (p.101). It has been given as the hydrochloride orally, by injection, or rectally, sometimes with an antispasmodic.

◊ References.

1. Al-Shurbaji A, Tokics L. The pharmacokinetics of ketobemidone in critically ill patients. *Br J Clin Pharmacol* 2002 **54:** 583–6.
2. Jylli L, *et al.* Comparison of the analgesic efficacy of ketobemidone and morphine for management of postoperative pain in children: a randomized, controlled study. *Acta Anaesthesiol Scand* 2004; **48:** 1256–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Ketodur†; ***Norw.:*** Ketodur†; Ketorax; ***Swed.:*** Ketodur†; Ketogan Novum.
Multi-ingredient: ***Denm.:*** Ketogan; ***Norw.:*** Ketogan; ***Swed.:*** Ketogan.

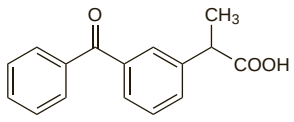
Ketoprofen *(BAN, USAN, rINN)*

Ketoprofeeni; Ketoprofén; Ketoprofenas; Kétoprofène; Ketoprofeno; Ketoprofenum; RP-19583. (*RS*)-2-(3-Benzoylphenyl)propionic acid.

Кетопрофен

$C_{16}H_{14}O_3$ = 254.3.

CAS — 22071-15-4 (ketoprofen); 57469-78-0 (ketoprofen lysine); 57495-14-4 (ketoprofen sodium).
ATC — M01AE03; M02AA10.
ATC Vet — QM01AE03; QM02AA10.



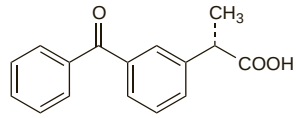
Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Ketoprofen). A white or almost white, crystalline powder. M.p. 94° to 97°. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.
USP 31 (Ketoprofen). Store in airtight containers.

Dexketoprofen Trometamol *(BANM, rINNM)*

(*S*)-(+)-Dexketoprofen Trometamol; Dexkétoprofène Trométamol; Dexketoprofeno trometamol; Dexketoprofenum Trometamolum.

Декскетопрофен Трометамол

CAS — 22161-81-5 (dexketoprofen).
ATC — M01AE17.
ATC Vet — QM01AE17.



(dexketoprofen)

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

When ketoprofen is given intramuscularly there may be pain at the injection site and occasionally tissue damage. Topical preparations containing ketoprofen may cause application site reactions. Ketoprofen suppositories may cause local irritation; rectal use should be avoided in patients with a history of proctitis or haemorrhoids. Ketoprofen should be used with caution in patients with renal or hepatic impairment; it should not be used in those with severe renal impairment.

Dexketoprofen should be avoided in patients with moderate to severe renal or severe hepatic impairment, and in those with severe heart failure.

Effects on the skin. Contact and photoallergic dermatitis has been seen after topical use of ketoprofen.[1,2] A retrospective study[3] found that of the 139 cases of contact reactions to topical NSAIDs reported to the Spanish Pharmacovigilance System between 1996 and 2001, 84 involved ketoprofen (16 allergy; 68 photoallergy). Totals for other NSAIDs included piroxicam (21), etofenamate (10), piketoprofen (5), salicylates (4), fepradinol (3), diclofenac (3), indometacin (2). phenylbutazone (2), benzydamine (2), aceclofenac (1), naproxen (1), and mabuprofen (1). Analysis indicated that the number of reports for topical ketoprofen was disproportionately high in relation to its usage.

1. Matthieu L, *et al.* Contact and photocontact allergy to ketoprofen: the Belgian experience. *Contact Dermatitis* 2004; **50:** 238–41.
2. Hindsén M, *et al.* Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; **54:** 150–7.
3. Diaz RL, *et al.* Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; **54:** 239–43.

Hypersensitivity. Life-threatening asthma, urticaria, and angioedema developed in 2 aspirin-sensitive patients after taking ketoprofen 50 mg by mouth.[1] Cardiac and respiratory arrest occurred in an asthmatic patient shortly after taking ketoprofen.[2] Life-threatening asthma has also occurred after topical application of ketoprofen.[3]

There has been a report[4] of delayed skin hypersensitivity in a patient who used a topical gel containing ketoprofen. The reaction recurred on rechallenge to ketoprofen gel but not to a similar gel containing diclofenac. The authors of the report noted that the UK CSM had received 15 reports of skin reactions to ketoprofen gel, including two each of dermatitis and urticaria.

See also Effects on the Skin, above.

1. Frith P, *et al.* Life-threatening asthma, urticaria, and angioœdema after ketoprofen. *Lancet* 1978; **ii:** 847–8.
2. Schreuder G. Ketoprofen: possible idiosyncratic acute bronchospasm. *Med J Aust* 1990; **152:** 332–3.
3. Kashiwabara K, Nakamura H. Analgesic-induced asthma caused by 2.0% ketoprofen adhesive agents, but not by 0.3% agents. *Intern Med* 2001; **40:** 124–6.
4. Oh VMS. Ketoprofen gel and delayed hypersensitivity dermatitis. *BMJ* 1994; **309:** 512.

Myasthenia gravis. There has been a brief report[1] of a cholinergic crisis precipitated by a single oral dose of ketoprofen 50 mg in a patient with well-controlled myasthenia gravis. The patient had previously noted a similar but milder reaction with aspirin, but not with paracetamol.

1. McDowell IFW, McConnell JB. Cholinergic crisis in myasthenia gravis precipitated by ketoprofen. *BMJ* 1985; **291:** 1094.

Pancreatitis. Pancreatitis has been associated with ketoprofen use.[1,2]

1. Cobb TK, Pierce JR. Acute pancreatitis associated with ketoprofen. *South Med J* 1992; **85:** 430–1.
2. Mété D, *et al.* Pancréatite aiguë et kétoprofène. *Gastroenterol Clin Biol* 2001; **25:** 721–2.

Photosensitivity. Ketoprofen causes photosensitivity reactions[1,2] and cross-sensitivity to other drugs, notably the fibrates bezafibrate, ciprofibrate, and fenofibrate, has also been reported. The cross reactions were attributed to the benzoyl ketone structure that the drugs have in common.

See also Effects on the Skin (above).

1. Bagheri H, *et al.* Photosensitivity to ketoprofen: mechanisms and pharmacoepidemiological data. *Drug Safety* 2000; **22:** 339–49.
2. Veyrac G, *et al.* Bilan de l'enquête nationale sur les effets indésirables cutanés du kétoprofène gel enregistrés entre le 01/09/1996 et le 31/08/2000. *Therapie* 2002; **57:** 55–64.

Renal impairment. The elimination half-life and unbound plasma concentrations of dexketoprofen are increased in patients with renal impairment given racemic ketoprofen;[1,2] this appears to be principally attributable to impaired renal clearance of the acyl-glucuronide conjugates in a stereoselective fashion, with subsequent hydrolysis of the unstable conjugate back to the aglycone producing increased plasma-ketoprofen concentrations.[2,3] The authors of one study suggested[3] that dosage adjustments of racemic ketoprofen were indicated only for patients with moderately severe renal failure (creatinine clearance of less than 20 mL/minute).

For advice on the dose of dexketoprofen in patients with renal impairment see under Uses and Administration, below. See also Adverse Effects and Precautions, above.

1. Hayball PJ, *et al.* The influence of renal function on the enantioselective pharmacokinetics and pharmacodynamics of ketoprofen in patients with rheumatoid arthritis. *Br J Clin Pharmacol* 1993; **36:** 185–93.
2. Grubb NG, *et al.* Stereoselective pharmacokinetics of ketoprofen and ketoprofen glucuronide in end-stage renal disease: evidence for a 'futile cycle' of elimination. *Br J Clin Pharmacol* 1999; **48:** 494–500.
3. Skeith KJ, *et al.* The influence of renal function on the pharmacokinetics of unchanged and acyl-glucuroconjugated ketoprofen enantiomers after 50 and 100 mg racemic ketoprofen. *Br J Clin Pharmacol* 1996; **42:** 163–9.

Interactions

For interactions associated with NSAIDs, see p.99.

Probenecid delays the excretion of ketoprofen and decreases its extent of protein binding resulting in increased plasma-ketoprofen concentrations. Not unexpectedly, a similar interaction may be seen with dexketoprofen and probenecid.

Pharmacokinetics

Ketoprofen is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur about 0.5 to 2 hours after an oral dose. When ketoprofen is given with food, the bioavailability is not altered but the rate of absorption is slowed. Ketoprofen is well absorbed from the intramuscular and rectal routes; only a small amount of percutaneous absorption occurs after topical application. Ketoprofen is 99% bound to plasma proteins and substantial concentrations of drug are found in the synovial fluid. The elimination half-life in plasma is about 1.5 to 4 hours. Ketoprofen is metabolised mainly by conjugation with glucuronic acid, and is excreted mainly in the urine.

Ketoprofen possesses a chiral centre. It is usually given as the racemate but its pharmacological actions appear to be due largely to the (*S*)-enantiomer, dexketoprofen. The pharmacokinetics of ketoprofen appear to exhibit little stereoselectivity (but see under Renal Impairment, above).

◊ References.

1. Debruyne D, *et al.* Clinical pharmacokinetics of ketoprofen after single intravenous administration as a bolus or infusion. *Clin Pharmacokinet* 1987; **12:** 214–21.
2. Flouvat B, *et al.* Pharmacokinetics of ketoprofen in man after repeated percutaneous administration. *Arzneimittelforschung* 1989; **39:** 812–15.
3. Jamali F, Brocks DR. Clinical pharmacokinetics of ketoprofen and its enantiomers. *Clin Pharmacokinet* 1990; **19:** 197–217.
4. Geisslinger G, *et al.* Pharmacokinetics of ketoprofen enantiomers after different doses of the racemate. *Br J Clin Pharmacol* 1995; **40:** 73–5.
5. Barbanoj MJ, *et al.* Pharmacokinetics of dexketoprofen trometamol in healthy volunteers after single and repeated oral doses. *J Clin Pharmacol* 1998; **38:** 33S–40S.
6. Kokki H, *et al.* Pharmacokinetics of ketoprofen syrup in small children. *J Clin Pharmacol* 2000; **40:** 354–9.
7. Barbanoj M-J, *et al.* Clinical pharmacokinetics of dexketoprofen. *Clin Pharmacokinet* 2001; **40:** 245–62.
8. Kokki H, *et al.* Pharmacokinetics of intravenous and rectal ketoprofen in young children. *Clin Pharmacokinet* 2003; **42:** 373–9.
9. Valles J, *et al.* Clinical pharmacokinetics of parenteral dexketoprofen trometamol in healthy subjects. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl A): 7–12.
10. Valles J, *et al.* Single and repeated dose pharmacokinetics of dexketoprofen trometamol in young and elderly subjects. *Methods Find Exp Clin Pharmacol* 2006; **28** (suppl A): 13–19.

Uses and Administration

Ketoprofen, a propionic acid derivative, is an NSAID (p.99). Its anti-inflammatory properties may be weaker than those of some other NSAIDs. Ketoprofen is a racemic mixture; in *animal* studies the S-(+) enantiomer, dexketoprofen, has about twice the analgesic activity of ketoprofen by weight.

Ketoprofen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and

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).

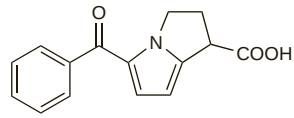
Кеторолак Трометамол

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