

## 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; Ketobemidoni hydrokloridi; Ketobemidono hydrochloridas. 1-(4-m-Hydroxyphenyl)-1-methyl-4-piperidyl)propan-1-one hydrochloride.

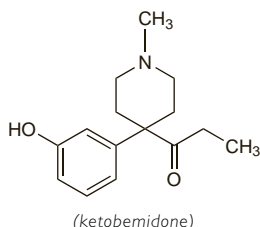
Кетобемидона Гидрохлорид

C<sub>15</sub>H<sub>21</sub>NO<sub>3</sub>·HCl = 283.8.

CAS — 469-79-4 (ketobemidone); 5965-49-1 (ketobemidone hydrochloride).

ATC — N02AB01.

ATC Vet — QN02AB01.



**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)

Ketoprofeni; Ketoprófen; Ketoprofenas; Kétoproféne; Ketoprofeno; Ketoprofenum; RP-19583. (RS)-2-(3-Benzoylphenyl)propionic acid.

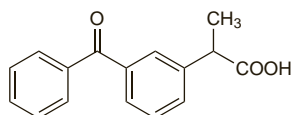
Кетопрофен

C<sub>16</sub>H<sub>14</sub>O<sub>3</sub> = 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; Dextétoproféne Trométamol; Dextetoprofeno trometamol; Dextetoprofenum Trometamol.

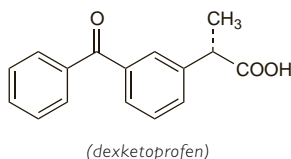
Декскетопрофен Трометамол

CAS — 22161-81-5 (dexketoprofen).

ATC — M01AE17.

ATC Vet — QM01AE17.

The symbol † denotes a preparation no longer actively marketed



## 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.<sup>1,2</sup> A retrospective study<sup>3</sup> 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.<sup>1</sup> Cardiac and respiratory arrest occurred in an asthmatic patient shortly after taking ketoprofen.<sup>2</sup> Life-threatening asthma has also occurred after topical application of ketoprofen.<sup>3</sup>

There has been a report<sup>4</sup> of delayed skin hypersensitivity in a patient who used a topical gel containing ketoprofen. The reaction occurred 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 angioedema 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<sup>1</sup> 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.<sup>1,2</sup>

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 kétoproféne. *Gastroenterol Clin Biol* 2001; **25**: 721–2.

**Photosensitivity.** Ketoprofen causes photosensitivity reactions<sup>1,2</sup> 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 pharmacopeidemiological data. *Drug Safety* 2000; **22**: 339–49.
2. Veyrac G, *et al.* Bilan de l'enquête nationale sur les effets indésirables cutanés du kétoproféne gel enregistrés entre le 01/09/1996 et le 31/08/2000. *Thérapie* 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;<sup>1,2</sup> 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.<sup>2,3</sup> The authors of one study suggested<sup>3</sup> 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, Brooks 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. Barbanjo MJ, *et al.* Pharmacokinetics of dexketoprofen trometamol in healthy volunteers after single and repeated oral doses. *J Clin Pharmacol* 1998; **38**: 335–40S.
6. Kokki H, *et al.* Pharmacokinetics of ketoprofen syrup in small children. *J Clin Pharmacol* 2000; **40**: 354–9.
7. Barbanjo MJ, *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