tations of moderately to severely active ulcerative colitis is under review by NICE.

1. Present DH, *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340:** 1398–405.
2. Rutgeerts P, *et al.* Efficacy and safety of retreatment with antitumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117:** 761–9.
3. Hanauer SB, *et al.* ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359:** 1541–9.
4. Rutgeerts P, *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; **126:** 402–13.
5. Sands BE, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350:** 876–85.
6. Panaccione R, *et al.* Canadian Association of Gastroenterology Clinical Practice Guidelines: the use of infliximab in Crohn's disease. *Can J Gastroenterol* 2004; **18:** 503–8. Also available at: http://www.cag-acg.org/uploads/guidelines/Infliximab%20guidelines%202004.pdf (accessed 13/06/08)
7. Siddiqui MAA, Scott LJ. Infliximab: a review of its use in Crohn's disease and rheumatoid arthritis. *Drugs* 2005; **65:** 2179–2208. Correction. *ibid.* 2006; **66:** 1359.
8. Rutgeerts P, *et al.* Review article: infliximab therapy for inflammatory bowel disease — seven years on. *Aliment Pharmacol Ther* 2006; **23:** 451–63.
9. Rutgeerts P, *et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63:** 433–42.
10. Lémann M, *et al.* Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif (GETAID). Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006; **130:** 1054–61.
11. Osterman MT, Lichtenstein GR. Infliximab in fistulizing Crohn's disease. *Gastroenterol Clin North Am* 2006; **35:** 795–820.
12. Probert CS, *et al.* Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003; **52:** 998–1002.
13. Rutgeerts P, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353:** 2462–76. Correction. *ibid.* 2006; **354:** 2200.
14. Lawson MM, *et al.* Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
15. Aberra FN, Lichtenstein GR. Infliximab in ulcerative colitis. *Gastroenterol Clin North Am* 2006; **35:** 821–36.
16. Gisbert JP, *et al.* Systematic review: Infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007; **25:** 19–37.
17. Baldassano R, *et al.* Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. *Am J Gastroenterol* 2003; **98:** 833–8.
18. Hyams J, *et al.* REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; **132:** 863–73.
19. de Ridder L, *et al.* Infliximab use in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **45:** 3–14.
20. Veres G, *et al.* Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs* 2007; **67:** 1703–23.
21. NICE. Guidance on the use of infliximab for Crohn's disease: Technology Appraisal Guidance 40 (issued April 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/NiceCROHNS40GUIDANCE.pdf (accessed 13/06/08)
22. NICE. Infliximab for subacute manifestations of ulcerative colitis: Technology Appraisal Guidance 140 (issued April 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA140Guidance.pdf (accessed 28/07/08)

Leprosy. Infliximab has been used[1] in the treatment of recurrent type 2 (erythema nodosum leprosum) lepra reactions (see Leprosy, p.176). However, 2 cases of rapidly progressive leprosy developing in patients given infliximab for rheumatoid arthritis have also been described;[2] reversal (type 1) reactions occurred in both when infliximab was stopped.

1. Faber WR, *et al.* Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med* 2006; **355:** 739.
2. Scollard DM, *et al.* Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. *Clin Infect Dis* 2006; **43:** e19–e22.

Psoriasis. Infliximab is used in the treatment of moderate to severe plaque psoriasis (p.1583).[1-8] In the UK, NICE recommends[8] that it be reserved for severe cases, unresponsive to standard therapies (including ciclosporin, methotrexate, and PUVA) or where such therapies cannot be used.

1. Benoit S, *et al.* Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. *Br J Dermatol* 2004; **150:** 1009–12.
2. Gottlieb AB, *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51:** 534–42.
3. Reich K, *et al.* EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366:** 1367–74.
4. Reich K, *et al.* Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154:** 1161–8.
5. Smith CH, *et al.* Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 2006; **155:** 160–9.
6. Menter A, *et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2006; **56:** 31.e1–15.
7. Poulalhon N, *et al.* A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. *Br J Dermatol* 2007; **156:** 329–36.
8. NICE. Infliximab for the treatment of adults with psoriasis: Technology Appraisal Guidance 134 (issued January 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA134Guidance.pdf (accessed 22/08/08)

Rheumatoid arthritis. TNF inhibitors play an increasingly important role in the management of rheumatoid arthritis; they tend to be reserved for patients who are unresponsive to more conventional disease-modifying drugs, although some favour use earlier in management.

Some references to the use of infliximab in rheumatoid arthritis (p.11) and juvenile idiopathic arthritis (p.10).

1. Maini R, *et al.* ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; **354:** 1932–9.
2. Lipsky PE, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1594–1602.
3. Maini RN, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004; **50:** 1051–65.
4. Quinn MA, *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 27–35.
5. Voulgari PV, *et al.* Infliximab therapy in established rheumatoid arthritis: an observational study. *Am J Med* 2005; **118:** 515–20.
6. Ruperto N, *et al.* Paediatric Rheumatology International Trials Organisation. Pediatric Rheumatology Collaborative Study Group. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007; **56:** 3096–3106.
7. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)

Sarcoidosis. For a mention of possible benefit from infliximab in sarcoidosis, see p.1512.

Spondyloarthropathies. References to the use of infliximab in the treatment of ankylosing spondylitis and psoriatic arthritis (p.13). In the UK, NICE considers that TNF inhibitors should be reserved for severe active psoriatic arthritis unresponsive to at least 2 standard disease-modifying drugs; etanercept or adalimumab are preferred to infliximab.

1. Brandt J, *et al.* Infliximab in the treatment of active and severe ankylosing spondylitis. *Clin Exp Rheumatol* 2002; **20** (Suppl 28): S106–S110.
2. Brandt J, *et al.* Successful short term treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor-alpha monoclonal antibody infliximab. *J Rheumatol* 2002; **29:** 118–22.
3. Collantes-Estévez E, *et al.* Infliximab in refractory spondyloarthropathies: a multicentre 38 week open study. *Ann Rheum Dis* 2003; **62:** 1239–40.
4. Robinson DM, Keating GM. Infliximab: in ankylosing spondylitis. *Drugs* 2005; **65:** 1283–91.
5. NICE. Etanercept and infliximab for the treatment of adults with psoriatic arthritis: Technology Appraisal Guidance 104 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA104guidance.pdf (accessed 13/06/08)
6. Rott S, *et al.* Successful treatment of severe psoriatic arthritis with infliximab in an 11-year-old child suffering from linear psoriasis along lines of Blaschko. *Br J Dermatol* 2007; **157:** 191–2.

Uveitis. Infliximab has been tried with some success in the treatment of uveitis (p.1515) including that associated with Behçet's syndrome (p.1499). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with infliximab may improve ocular symptoms in addition to its effect on the primary disorder.

References.

1. Murphy CC, *et al.* Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. *Ophthalmology* 2004; **111:** 352–6.
2. Bodaghi B, *et al.* Therapeutic use of infliximab in sight threatening uveitis: retrospective analysis of efficacy, safety, and limiting factors. *Ann Rheum Dis* 2005; **64:** 962–4.
3. Braun J, *et al.* Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; **52:** 2447–51.
4. Richards JC, *et al.* Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Experiment Ophthalmol* 2005; **33:** 461–8.
5. Lindstedt EW, *et al.* Anti-TNF-α therapy for sight threatening uveitis. *Br J Ophthalmol* 2005; **89:** 533–6.
6. Saurenmann RK, *et al.* Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006; **45:** 982–9.
7. Kahn P, *et al.* Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006; **113:** 860–4.e2.
8. Guignard S, *et al.* Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 2006; **65:** 1631–4.
9. Tynjälä P, *et al.* Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2007; **66:** 548–50.
10. Ardoin SP, *et al.* Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. *Am J Ophthalmol* 2007; **144:** 844–849.
11. Pipitone N, *et al.* Infliximab for the treatment of Neuro-Behçet's disease: a case series and review of the literature. *Arthritis Rheum* 2008; **59:** 285–90.

Vasculitic syndromes. For a preliminary report on the use of infliximab in Takayasu's arteritis, see p.1514. Infliximab has also been investigated in the management of Kawasaki disease (p.2228) in patients who are unresponsive to standard treatment.[1-3]

1. Burns JC, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.
2. Saji T, Kemmotsu Y. Infliximab for Kawasaki syndrome. *J Pediatr* 2006; **149:** 426.
3. O'Connor MJ, Saulsbury FT. Incomplete and atypical Kawasaki disease in a young infant: severe, recalcitrant disease responsive to infliximab. *Clin Pediatr (Phila)* 2007; **46:** 345–8.

Preparations

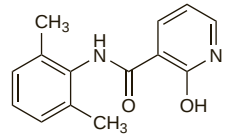
Proprietary Preparations (details are given in Part 3)
Arg.: Remicade†; Revellex†; ***Austral.:*** Remicade; ***Belg.:*** Remicade; ***Braz.:*** Remicade; ***Canad.:*** Remicade; ***Chile:*** Remicade; ***Cz.:*** Remicade; ***Denm.:*** Remicade; ***Fin.:*** Remicade; ***Fr.:*** Remicade; ***Ger.:*** Remicade; ***Gr.:*** Remicade; ***Hong Kong:*** Remicade; ***Hung.:*** Remicade; ***Indon.:*** Remicade; ***Irl.:*** Remicade; ***Israel:*** Remicade; ***Ital.:*** Remicade; ***Jpn:*** Remicade; ***Malaysia:*** Remicade; ***Mex.:*** Remicade; ***Neth.:*** Remicade; ***Norw.:*** Remicade; ***NZ:*** Remicade; ***Philipp.:*** Remicade; ***Pol.:*** Remicade; ***Port.:*** Remicade; ***Rus.:*** Remicade (Ремикейд); ***S.Afr.:*** Revellex; ***Singapore:*** Remicade; ***Spain:*** Remicade; ***Swed.:*** Remicade; ***Switz.:*** Remicade; ***Thai.:*** Remicade; ***Turk.:*** Remicade; ***UK:*** Remicade; ***USA:*** Remicade; ***Venez.:*** Remicade.

Isonixin *(rINN)*

Isonixine; Isonixino; Isonixinum. 2-Hydroxy-*N*-(2,6-dimethylphenyl)nicotinamide.

Изониксин

$C_{14}H_{14}N_2O_2$ = 242.3.
CAS — 57021-61-1.



Profile
Isonixin is an NSAID (p.96) that has been used in the management of pain and inflammation associated with musculoskeletal and joint disorders. It has been used in doses of 400 mg two to four times daily by mouth or by rectal suppository. It has also been applied topically as a 2.5% cream.

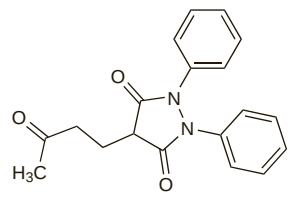
Preparations
Proprietary Preparations (details are given in Part 3)
Spain: Nixyn.
Multi-ingredient: ***Spain:*** Nixyn.

Kebuzone *(rINN)*

Kebuzona; Kébuzone; Kebuzonum; Ketophenylbutazone. 4-(3-Oxobutyl)-1,2-diphenylpyrazolidine-3,5-dione.

Кебузон

$C_{19}H_{18}N_2O_3$ = 322.4.
CAS — 853-34-9.
ATC — M01AA06.
ATC Vet — QM01AA06.



Profile
Kebuzone, a phenylbutazone derivative, is an NSAID (p.96). It has been given for musculoskeletal, joint, and soft-tissue disorders in oral doses of up to 1.5 g daily in divided doses. Kebuzone has also been given as the sodium salt by intramuscular injection in doses equivalent to 1 g of base once or twice daily.

Porphyria. Kebuzone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.

Preparations

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

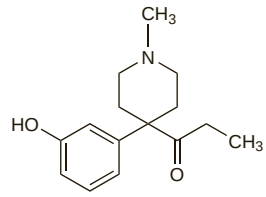
Ketobemidone Hydrochloride *(BANM, rINNM)*

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.

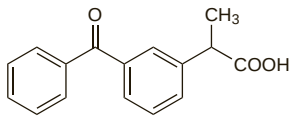
Ketoprofen *(BAN, USAN, rINN)*

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.



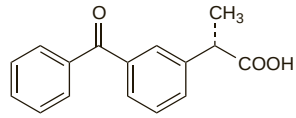
Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Ketoprofen). A white or almost white, crystalline powder. M.p. 94° to 97°. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane.
USP 31 (Ketoprofen). Store in airtight containers.

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).

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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