tient's daily requirement. The mean dose of diamorphine required for stabilisation was 55 mg compared with 36 mg for methadone. Some centres have given diamorphine in the form of reefers. Diamorphine has also been prescribed with methadone in the management of addicts.[2] A systematic review[3] that included this study failed to produce conclusive results about the effectiveness of diamorphine (alone or with methadone) in maintenance treatment; however, since the studies were not directly comparable, continued evaluation in clinical studies is required. Oral tablets[4] and intravenous injection[5] of diamorphine have also been tried in severely dependent, treatment-resistant patients.

Breast feeding has been used to treat diamorphine dependence in the offspring of dependent mothers but this is no longer considered to be the best method and some authorities recommend that breast feeding should be stopped.

1. Ghodse AH, *et al.* Comparison of oral preparations of heroin and methadone to stabilise opiate misusers as inpatients. *BMJ* 1990; **300:** 719–20.
2. van den Brink W, *et al.* Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. Abridged version: *BMJ* 2003; **327:** 310–12. Correction. *ibid.*; 724. Full version: http://www.bmj.com/cgi/reprint/327/7410/310 (accessed 26/06/08)
3. Ferri M, *et al.* Heroin maintenance for chronic heroin dependents. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 26/06/08).
4. Frick U, *et al.* A prospective cohort study on orally administered heroin substitution for severely addicted opioid users. *Addiction* 2006; **101:** 1631–9.
5. March JC, *et al.* Controlled trial of prescribed heroin in the treatment of opioid addiction. *J Subst Abuse Treat* 2006; **31:** 203–11.

Pain. ***ACUTE PAIN.*** Rapid pain relief may be obtained with the intravenous injection of diamorphine. Other routes include the intraspinal route for which diamorphine is well suited because of its lipid solubility and pharmacokinetics. Epidural doses of diamorphine have ranged from 0.5 to 10 mg.[1] Analgesia was significantly more prolonged and more intense after epidural rather than intramuscular injection of diamorphine 5 mg in women who had had caesarean section;[2] itching was reported by 50% of patients undergoing epidural analgesia. Epidural diamorphine alone[3] or with bupivacaine[4] has been used for analgesia during labour; addition of adrenaline appeared to improve the quality and duration of analgesia with diamorphine.[3] In another study addition of diamorphine to bupivacaine produced a high incidence of pruritus and drowsiness.[5] A study[6] of patient-controlled analgesia for postoperative pain found that although epidural diamorphine, used alone or with bupivacaine, reduced the analgesic dose requirement, there was little clinical advantage over the subcutaneous route.

Continuous epidural infusion of diamorphine 500 micrograms/hour in 0.125% bupivacaine provided postoperative analgesia superior to that with either drug alone in patients undergoing major abdominal gynaecological surgery.[7] A similar infusion produced analgesia superior to that with either epidural bolus injection or patient-controlled intravenous diamorphine in patients undergoing total abdominal hysterectomy.[8] However, more patients receiving the continuous epidural infusion were hypoxaemic than in the other 2 groups.

Diamorphine has also been given intrathecally for postoperative analgesia and should be effective at lower doses than with the epidural route because of greater CSF concentrations. Diamorphine 250 or 500 micrograms given intrathecally with bupivacaine spinal anaesthesia both provided greater postoperative analgesia than bupivacaine alone,[9] but the incidence of adverse effects, especially nausea, vomiting, and urinary retention, was still high with either dose and routine use of this technique was not recommended. Intrathecal diamorphine with bupivacaine has also been used for analgesia during labour[10,11] and caesarean section.[12-16] In a study[12] in patients undergoing caesarean section, intrathecal diamorphine 250 micrograms showed comparable postoperative analgesia with a 5-mg epidural dose and was associated with less postoperative nausea and vomiting. Other studies[13,14] found that intrathecal diamorphine reduced supplemental analgesic requirements during and after caesarean section when compared with intrathecal fentanyl. Intrathecal diamorphine 400 micrograms was considered by some[15] to be the lowest dose required to reduce intraoperative analgesic supplementation to below 5%; however, lower doses of 300 micrograms have been used in practice.[16]

Diamorphine has been extensively used by cardiologists in the UK for the management of pain in acute left ventricular failure, unstable angina, and myocardial infarction. It has been theorised that diamorphine may offer benefits over morphine because its stimulatory effects at opioid δ receptors on the myocardium may reduce the extent of myocardial damage.[17] Evidence to support this theory is, however, lacking.

1. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
2. Macrae DJ, *et al.* Double-blind comparison of the efficacy of extradural diamorphine, extradural phenoperidine and im diamorphine following caesarean section. *Br J Anaesth* 1987; **59:** 354–9.
3. Keenan GMA, *et al.* Extradural diamorphine with adrenaline in labour: comparison with diamorphine and bupivacaine. *Br J Anaesth* 1991; **66:** 242–6.
4. McGrady EM, *et al.* Epidural diamorphine and bupivacaine in labour. *Anaesthesia* 1989; **44:** 400–3.
5. Bailey CR, *et al.* Diamorphine-bupivacaine mixture compared with plain bupivacaine for analgesia. *Br J Anaesth* 1994; **72:** 58–61.
6. Gopinathan C, *et al.* A comparative study of patient-controlled epidural diamorphine, subcutaneous diamorphine and an epidural diamorphine/bupivacaine combination for postoperative pain. *Eur J Anaesthesiol* 2000; **17:** 189–96.
7. Lee A, *et al.* Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988; **60:** 845–50.
8. Madej TH, *et al.* Hypoxaemia and pain relief after lower abdominal surgery: comparison of extradural and patient-controlled analgesia. *Br J Anaesth* 1992; **69:** 554–7.
9. Reay BA, *et al.* Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery. *Br J Anaesth* 1989; **62:** 248–52.
10. Kestin IG, *et al.* Analgesia for labour and delivery using incremental diamorphine and bupivacaine via a 32-gauge intrathecal catheter. *Br J Anaesth* 1992; **68:** 244–7.
11. Vaughan DJA, *et al.* Choice of opioid for initiation of combined spinal epidural analgesia in labour—fentanyl or diamorphine. *Br J Anaesth* 2001; **86:** 567–9.
12. Hallworth SP, *et al.* Comparison of intrathecal and epidural diamorphine for elective Caesarean section using a combined spinal-epidural technique. *Br J Anaesth* 1999; **82:** 228–32.
13. Cowan CM, *et al.* Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia. *Br J Anaesth* 2002; **89:** 452–8.
14. Lane S, *et al.* A comparison of intrathecal fentanyl and diamorphine as adjuncts in spinal anaesthesia for Caesarean section. *Anaesthesia* 2005; **60:** 453–7.
15. Saravanan S, *et al.* Minimum dose of intrathecal diamorphine required to prevent intraoperative supplementation of spinal anaesthesia for Caesarean section. *Br J Anaesth* 2003; **91:** 368–72.
16. Wrench IJ, *et al.* Dose response to intrathecal diamorphine for elective caesarean section and compliance with a national audit standard. *Int J Obstet Anesth* 2007; **16:** 17–21.
17. Poullis M. Diamorphine and British cardiology: so we are right! *Heart* 1999; **82:** 645–6.

CHRONIC PAIN. Patients with chronic opioid-sensitive pain are often treated with diamorphine given by continuous subcutaneous infusion using a small battery-operated syringe driver. The following technique has been described.[1] Diamorphine hydrochloride 1 g could be dissolved in 1.6 mL of water to give a solution with a volume of 2.4 mL (415 mg/mL), but the maximum suggested concentration was 250 mg/mL. If the analgesic requirement was not known the following protocol was recommended:

- Start injections every 4 hours of 2.5 or 5 mg diamorphine, or, if the patient has already been taking opioids, a dose that is equivalent to the last dose
- If this is unsatisfactory increase this dose in 50% increments until the patient reports even a little pain relief
- Calculate the 24-hour requirement by multiplying by six, and start the infusion at this level
- Increase the 24-hour dosage in the pump by 50% increments until the pain is controlled. Note that requirements may vary from less than 20 mg to more than 5 g per 24 hours

When starting an infusion it is important not to allow any breakthrough pain. This may be achieved either by starting the infusion more than 2 hours before the previous oral dose wears off or by giving a loading dose injection of the 4-hourly requirement.

Although generally free from complications, sterile abscess formation was reported in 2 patients with advanced cancer receiving diamorphine by continuous subcutaneous infusions.[2]

The intraspinal[3] and intraventricular[4] routes have also been used successfully in patients with intractable pain. Topical application of diamorphine has also been tried[5,6] for the control of pressure ulcer pain in a small number of palliative care patients.

1. Dover SB. Syringe driver in terminal care. *BMJ* 1987; **294:** 553–5.
2. Hoskin PJ, *et al.* Sterile abscess formation by continuous subcutaneous infusion of diamorphine. *BMJ* 1988; **296:** 1605.
3. Baker L, *et al.* Evolving spinal analgesia practice in palliative care. *Palliat Med* 2004; **18:** 507–15.
4. Reeve WG, Todd JG. Intraventricular diamorphine via an Ommaya shunt for intractable cancer pain. *Br J Anaesth* 1990; **65:** 544–7.
5. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage* 2003; **25:** 547–54.
6. Abbas SQ. Diamorphine-Intrasite dressings for painful pressure ulcers. *J Pain Symptom Manage* 2004; **28:** 532–4.

Preparations

BP 2008: Diamorphine Injection;
BPC 1973: Diamorphine Linctus.

Proprietary Preparations (details are given in Part 3)
Switz.: Diaphin.

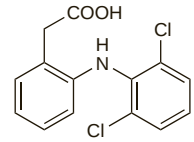
Diclofenac *(BAN, rINN)*

Diclofénac; Diclofenaco; Diclofenacum; Diklofenaakki; Diklofenak. [2-(2,6-Dichloroanilino)phenyl]acetic acid.

Диклофенак

$C_{14}H_{11}Cl_2NO_2 = 296.1$.

CAS — 15307-86-5.
ATC — D11AX18; M01AB05; M02AA15; S01BC03.
ATC Vet — QD11AX18; QM01AB05; QM02AA15; QS01BC03.



Diclofenac Diethylamine *(BANM)*

Diclofenac Diethylammonium; Diclofenaco dietilamina; Diklofenak Dietilamonyum.

Диклофенак Диэтиламин

$C_{18}H_{22}Cl_2N_2O_2 = 369.3$.

CAS — 78213-16-8.
ATC — D11AX18.
ATC Vet — QD11AX18.

Pharmacopoeias. In *Br.*

BP 2008 (Diclofenac Diethylamine). A white to light beige, crystalline powder. Sparingly soluble in water and in acetone; freely soluble in alcohol and in methyl alcohol; practically insoluble in 1M sodium hydroxide. The pH of a 1% solution in alcohol (10%) is between 6.4 and 8.4. Store in airtight containers. Protect from light.

Diclofenac Epolamine

DHEP; Diclofenac Hydroxyethylpyrrolidine.

Диклофенак Эполамин

$C_{14}H_{11}Cl_2NO_2$, $C_6H_{13}NO = 411.3$.

CAS — 119623-66-4.
ATC — D11AX18.
ATC Vet — QD11AX18.

Diclofenac Potassium *(BANM, USAN, rINNM)*

CGP-45840B; Diclofénac potassique; Diclofenaco potásico; Diclofenacum kalicum; Diklofenaakkikalium; Diklofenak draselná sůl; Diklofenak Potasyum; Diklofenakkalium; Diklofenák-kálium; Diklofenako kalio druska; Kalii Diclofenacum. Potassium [*o*-(2,6-dichloroanilino)phenyl]acetate.

Калия Диклофенак

$C_{14}H_{10}Cl_2KNO_2 = 334.2$.

CAS — 15307-81-0.
ATC — D11AX18.
ATC Vet — QD11AX18.

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

Ph. Eur. 6.2 (Diclofenac Potassium). A white or slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Diclofenac Potassium). pH of a 1% solution in water is between 7.0 and 8.5. Store at a temperature of 20° to 25°. Protect from light.

Diclofenac Sodium *(BANM, USAN, rINNM)*

Diclofénac sodique; Diclofenaco sódico; Diclofenacum natricum; Diclophenac Sodium; Diklofenaakkinatrium; Diklofenak sodná sůl; Diklofenak Sodyum; Diklofenaknatrium; Diklofenák-nátrium; Diklofenako natrio druska; GP-45840; Natrii Diclofenacum. Sodium [2-(2,6-dichloroanilino)phenyl]acetate.

Натрий Диклофенак

$C_{14}H_{10}Cl_2NNaO_2 = 318.1$.

CAS — 15307-79-6.
ATC — D11AX18.
ATC Vet — QD11AX18.

NOTE. DICL is a code approved by the BP 2008 for use on single unit doses of eye drops containing diclofenac sodium where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Diclofenac Sodium). A white to slightly yellowish, slightly hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 31 (Diclofenac Sodium). A white to off-white, hygroscopic, crystalline powder. Sparingly soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for NSAIDs in general, p.96.

There may be pain and, occasionally, tissue damage at the site of injection when diclofenac is given intramuscularly. Diclofenac suppositories can cause local irritation. Transient burning and stinging may occur with diclofenac ophthalmic solution; more serious corneal

adverse effects have also occurred (see Effects on the Eyes, below). Topical preparations of diclofenac, such as plasters and gel, may cause application site reactions.

Incidence of adverse effects. A review of worldwide clinical studies with diclofenac[1] has reported the incidence of drug-associated adverse effects to be about 12%; about 16% of patients who had adverse effects stopped treatment (a figure corresponding to about 2% of the entire patient sample). The most frequently reported adverse effects were gastrointestinal and were reported in 7.6% of patients. CNS-related adverse effects were reported in 0.7% of patients and allergy or local reactions in 0.4%. This and other reviews[2] have shown that adverse effects associated with diclofenac are usually mild and transient and appear to be unrelated to the dose given.

1. Willkens RF. Worldwide clinical safety experience with diclofenac. *Semin Arthritis Rheum* 1985; **15** (suppl 1): 105–10.
2. Small RE. Diclofenac sodium. *Clin Pharm* 1989; **8:** 545–8.

Effects on the blood. Results of a large survey undertaken to assess the relation between agranulocytosis, aplastic anaemia, and drug exposure indicated that diclofenac was significantly associated with aplastic anaemia, providing an estimated tenfold increase in risk.[1] There are reports of other haematological abnormalities including haemolytic anaemia,[2,3] thrombocytopenia,[4,5] neutropenia,[5] and agranulocytosis[6] occurring in patients given diclofenac.

Localised spontaneous bleeding,[7] bruising,[8] inhibition of platelet aggregation,[7] and prolonged bleeding time[8] have been reported.

1. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. *JAMA* 1986; **256:** 1749–57.
2. López A, *et al.* Autoimmune hemolytic anemia induced by diclofenac. *Ann Pharmacother* 1995; **29:** 787.
3. Ahrens N, *et al.* Misdiagnosis in patients with diclofenac-induced hemolysis: new cases and a concise review. *Am J Hematol* 2006; **81:** 128–31.
4. George S, Rahi AHS. Thrombocytopenia associated with diclofenac therapy. *Am J Health-Syst Pharm* 1995; **52:** 420–1.
5. Kim HL, Kovacs MJ. Diclofenac-associated thrombocytopenia and neutropenia. *Ann Pharmacother* 1995; **29:** 713–15.
6. Colomina P, Garcia S. Agranulocytosis caused by diclofenac. *DICP Ann Pharmacother* 1989; **23:** 507.
7. Price AJ, Obeid D. Spontaneous non-gastrointestinal bleeding associated with diclofenac. *Lancet* 1989; **ii:** 1520.
8. Khazan U, *et al.* Diclofenac sodium and bruising. *Ann Intern Med* 1990; **112:** 472–3.

Effects on the cardiovascular system. For a discussion of the cardiovascular effects of NSAIDs, including diclofenac, see p.96.

Effects on electrolytes. A syndrome resembling the syndrome of inappropriate antidiuretic hormone secretion has been reported in elderly women given diclofenac.[1,2] Also the UK CSM had received a report of fatal hyponatraemia in another elderly woman.[2]

1. Petersson I, *et al.* Water intoxication associated with non-steroidal anti-inflammatory drug therapy. *Acta Med Scand* 1987; **221:** 221–3.
2. Cheung NT, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by diclofenac. *BMJ* 1993; **306:** 186.

Effects on the eyes. A patient who had been taking oral diclofenac for several years and had increasingly complained of dry, gritty eyes noticed that eye irritation disappeared within 3 days when diclofenac had to be stopped because of gastrointestinal effects.[1]

Ocular diclofenac and related drugs have been implicated in reports of corneal toxicity. Ulceration of the conjunctiva or cornea, corneal or scleral melts, and perforations have been reported in patients using diclofenac eye drops, particularly after cataract surgery.[2-5] Keratitis and perforations were also reported with ketorolac eye drops,[4] although less frequently. For mention of corneal melting with bromfenac, see p.28.

1. Reid ALA, Henderson R. Diclofenac and dry, irritable eyes. *Med J Aust* 1994; **160:** 308.
2. Lin JC, *et al.* Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. *Arch Ophthalmol* 2000; **118:** 1129–32.
3. Congdon NG, *et al.* Corneal complications associated with topical ophthalmic use of nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg* 2001; **27:** 622–31.
4. Guidera AC, *et al.* Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. *Ophthalmology* 2001; **108:** 936–44.
5. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. *Trans Am Ophthalmol Soc* 2001; **99:** 205–10.

Effects on the gastrointestinal tract. The most frequent adverse effects reported in patients given diclofenac systemically are gastrointestinal in nature. Typical reactions include epigastric pain, nausea, vomiting, and diarrhoea. Rarely peptic ulcer and gastrointestinal bleeding have occurred. Diclofenac has also been implicated as the causative agent in colonic ulceration,[1] small bowel perforation,[2] and pseudomembranous colitis.[3] Diclofenac suppositories may cause local reactions such as itching, burning, or exacerbation of haemorrhoids.

1. Carson J, *et al.* Colonic ulceration and bleeding during diclofenac therapy. *N Engl J Med* 1990; **323:** 135.
2. Deakin M, *et al.* Small bowel perforation associated with an excessive dose of slow release diclofenac sodium. *BMJ* 1988; **297:** 488–9.
3. Gentric A, Pennec YL. Diclofenac-induced pseudomembranous colitis. *Lancet* 1992; **340:** 126–7.

Effects on the kidneys. Renal papillary necrosis[1] and nephrotic syndrome[2-4] have been reported in patients taking diclofenac. See also Effects on Electrolytes, above.

1. Scott SJ, *et al.* Renal papillary necrosis associated with diclofenac sodium. *BMJ* 1986; **292:** 1050.
2. Beun GDM, *et al.* Isolated minimal change nephropathy associated with diclofenac. *BMJ* 1987; **295:** 182–3.
3. Yinnon AM, *et al.* Nephrotic syndrome associated with diclofenac sodium. *BMJ* 1987; **295:** 556.
4. Tattersall J, *et al.* Membranous nephropathy associated with diclofenac. *Postgrad Med J* 1992; **68:** 392–3.

Effects on the liver. Elevations of serum aminotransferase activity and clinical hepatitis,[1-8] including fatal fulminant hepatitis[2,5] have occurred in patients taking diclofenac. There has also been a case report of hepato-renal damage attributed to diclofenac.[9] Analysis[10] of 180 of the cases of diclofenac-associated hepatic injury received by the FDA between November 1988 and June 1991 suggested an increased risk of hepatotoxicity in female patients and those taking diclofenac for osteoarthritis. Hepatotoxicity had been detected within 6 months of starting diclofenac in 85% of the patients. The biochemical pattern of injury was hepatocellular or mixed hepatocellular in 66% of patients and cholestatic injury was found in 8% of patients. Signs of hypersensitivity were uncommon and it was considered that the mechanism of hepatic injury was likely to be a metabolic idiosyncratic reaction rather than due to intrinsic toxicity of diclofenac.

1. Dunk AA, *et al.* Diclofenac hepatitis. *BMJ* 1982; **284:** 1605–6.
2. Breen EG, *et al.* Fatal hepatitis associated with diclofenac. *Gut* 1986; **27:** 1390–3.
3. Schapira D, *et al.* Diclofenac-induced hepatotoxicity. *Postgrad Med J* 1986; **62:** 63–5.
4. Ryley NG, *et al.* Diclofenac associated hepatitis. *Gut* 1989; **30:** A708.
5. Helfgott SM, *et al.* Diclofenac-associated hepatotoxicity. *JAMA* 1990; **264:** 2660–2.
6. Purcell P, *et al.* Diclofenac hepatitis. *Gut* 1991; **32:** 1381–5.
7. Bhogaraju A, *et al.* Diclofenac-associated hepatitis. *South Med J* 1999; **92:** 711–13.
8. Greaves RRSH, *et al.* Inadvertent diclofenac rechallenge from generic and non-generic prescribing, leading to liver transplantation for fulminant liver failure. *Eur J Gastroenterol Hepatol* 2001; **13:** 71–3.
9. Diggory P, *et al.* Renal and hepatic impairment in association with diclofenac administration. *Postgrad Med J* 1989; **64:** 507–8.
10. Banks AT, *et al.* Diclofenac-associated hepatotoxicity: analysis of 180 cases reported to the Food and Drug Administration as adverse reactions. *Hepatology* 1995; **22:** 820–7.

Effects on the skin. Self-limiting skin reactions such as rash or pruritus may occur in patients given diclofenac. More serious skin reactions attributed to diclofenac include bullous dermatitis[1] and erythema multiforme.[2,3] Local irritation and necrosis has occurred on intramuscular injection of diclofenac.[4-7]

1. Gabrielsen TØ, *et al.* Drug-induced bullous dermatosis with linear IgA deposits along the basement membrane. *Acta Derm Venereol (Stockh)* 1981; **61:** 439–41.
2. Morris BAP, Remtulla SS. Erythema multiforme major following use of diclofenac. *Can Med Assoc J* 1985; **133:** 665.
3. Young J. Erythema multiforme-like eruption as a result of 'Solaraze' treatment. *J Dermatol Treat* 2003; **14:** 189.
4. Stricker BHC, van Kasteren BJ. Diclofenac-induced isolated myonecrosis and the Nicolau syndrome. *Ann Intern Med* 1992; **117:** 1058.
5. Pillans PI, O'Connor N. Tissue necrosis and necrotising fasciitis after intramuscular administration of diclofenac. *Ann Pharmacother* 1995; **29:** 264–6.
6. Ezzedine K, *et al.* Nicolau syndrome following diclofenac administration. *Br J Dermatol* 2004; **150:** 385–7.
7. Mutalik S, Belgaumkar V. Nicolau syndrome: a report of 2 cases. *J Drugs Dermatol* 2006; **5:** 377–8.

Hypersensitivity. Aspirin-sensitive asthmatic patients have developed reactions (rhinorrhoea, tightness of chest, wheezing, dyspnoea) when challenged with diclofenac in doses of 10 to 25 mg[1] and the UK CSM has received a report of an aspirin-sensitive patient who died from acute asthma 4 hours after a single 25-mg dose of diclofenac.[2]

Anaphylactic shock has been reported.[3]

1. Szczeklik A, *et al.* Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *BMJ* 1977; **2:** 231–2.
2. CSM/MCA. Avoid all NSAIDs in aspirin-sensitive patients. *Current Problems* 1993; **19:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
3. Dux S, *et al.* Anaphylactic shock induced by diclofenac. *BMJ* 1983; **286:** 1861.

Precautions

As for NSAIDs in general, p.98. Systemic diclofenac is contra-indicated in patients with severe hepatic or renal impairment.

In addition, use of intravenous diclofenac is contra-indicated in patients with moderate or severe renal impairment, hypovolaemia, or dehydration; it should also not be given intravenously in patients with a history of haemorrhagic diathesis, cerebrovascular bleeding (including suspected), or asthma nor in patients undergoing surgery with a high risk of haemorrhage.

Ophthalmic preparations containing diclofenac should not be used by patients who wear soft contact lenses.

Breast feeding. Diclofenac is distributed into breast milk although the *BNF* and some licensed product information consider the amount to be too small to be harmful to breast-fed infants.

Porphyria. Diclofenac sodium has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Veterinary use. Veterinary use of diclofenac in cattle in South Asia has been associated with severe decline in the numbers of vultures, to whom the residues are highly toxic if they consume the carcasses.[1,2] Meloxicam (p.80) has been suggested as an alternative.

1. Shultz S, *et al.* Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. *Proc Biol Sci* 2004; **271** (suppl 6): S458–S460.
2. Sharp D. Meloxicam to prevent rabies? *Lancet* 2006; **367:** 887–8.

Interactions

For interactions associated with NSAIDs, see p.99.

Diclofenac should not be given intravenously to patients already receiving other NSAIDs or anticoagulants including low-dose heparin.

Ciclosporin. Deterioration in renal function has been attributed to the use of diclofenac with ciclosporin.[1] Increased concentrations of diclofenac were also noted with ciclosporin;[2] licensed product information for ciclosporin recommends that the dosage of diclofenac should be reduced by about one-half when the two are given together.

1. Branthwaite JP, Nicholls A. Cyclosporin and diclofenac interaction in rheumatoid arthritis. *Lancet* 1991; **337:** 252.
2. Kovarik JM, *et al.* Cyclosporine and nonsteroidal antiinflammatory drugs: exploring potential drug interactions and their implications for the treatment of rheumatoid arthritis. *J Clin Pharmacol* 1997; **37:** 336–43.

Diuretics. Deterioration in renal function has been attributed to the use of diclofenac with *triamterene*.[1]

1. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* 1986; **293:** 698–9.

Gastrointestinal drugs. A decrease in the plasma concentration of diclofenac has been reported[1] when given after *sucralfate*.

1. Pedrazzoli J, *et al.* Short-term sucralfate administration alters potassium diclofenac absorption in healthy male volunteers. *Br J Clin Pharmacol* 1997; **43:** 104–108.

Lipid regulating drugs. *Colestyramine* appears substantially to reduce the bioavailability of diclofenac when the two drugs are given together;[1] *colestipol* produces a similar but smaller effect.

1. al-Balla SR, *et al.* The effects of cholestyramine and colestipol on the absorption of diclofenac in man. *Int J Clin Pharmacol Ther* 1994; **32:** 441–5.

Misoprostol. The plasma concentration of diclofenac was reduced when it was given as a 100-mg dose daily in the form of a modified-release preparation to subjects receiving misoprostol 800 micrograms daily.[1] Use together was also associated with an increase in the incidence and severity of gastrointestinal effects. Studies by the manufacturer[2] had failed to find any significant pharmacokinetic interactions between diclofenac and misoprostol when given in a formulation containing diclofenac 50 mg and misoprostol 200 micrograms.

1. Dammann HG, *et al.* Differential effects of misoprostol and ranitidine on the pharmacokinetics of diclofenac and gastrointestinal symptoms. *Br J Clin Pharmacol* 1993; **36:** 345–9.
2. Karim A. Pharmacokinetics of diclofenac and misoprostol when administered alone or as a combination product. *Drugs* 1993; **45** (suppl 1): 7–14.

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

Pharmacokinetics

Diclofenac is rapidly absorbed when given as an oral solution, sugar-coated tablets, rectal suppository, or by intramuscular injection. It is absorbed more slowly when given as enteric-coated tablets, especially when this dosage form is given with food. Although diclofenac given orally is almost completely absorbed, it is subject to first-pass metabolism so that about 50% of the drug reaches the systemic circulation in the unchanged form. Diclofenac is also absorbed percutaneously. At therapeutic concentrations it is more than 99% bound to plasma proteins. Diclofenac penetrates synovial fluid where concentrations may persist even

when plasma concentrations fall; small amounts are distributed into breast milk. The terminal plasma half-life is about 1 to 2 hours. Diclofenac is metabolised to 4′-hydroxydiclofenac, 5-hydroxydiclofenac, 3′-hydroxydiclofenac and 4′,5-dihydroxydiclofenac. It is then excreted in the form of glucuronide and sulfate conjugates, mainly in the urine (about 60%) but also in the bile (about 35%); less than 1% is excreted as unchanged diclofenac.

◊ References.

1. Fowler PD, *et al.* Plasma and synovial fluid concentrations of diclofenac sodium and its major hydroxylated metabolites during long-term treatment of rheumatoid arthritis. *Eur J Clin Pharmacol* 1983; **25:** 389–94.
2. Maggi CA, *et al.* Comparative bioavailability of diclofenac hydroxyethylpyrrolidine vs diclofenac sodium in man. *Eur J Clin Pharmacol* 1990; **38:** 207–8.
3. Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac: therapeutic insights and pitfalls. *Clin Pharmacokinet* 1997; **33:** 184–213.
4. Brenner SS, *et al.* Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib. *Clin Pharmacokinet* 2003; **42:** 283–92.
5. Hinz B, *et al.* Bioavailability of diclofenac potassium at low doses. *Br J Clin Pharmacol* 2005; **59:** 80–4.

Uses and Administration

Diclofenac, a phenylacetic acid derivative, is an NSAID (p.99). It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions: musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis; peri-articular disorders such as bursitis and tendinitis; soft-tissue disorders such as sprains and strains; and other painful conditions such as renal colic, acute gout, dysmenorrhoea, migraine, and after some surgical procedures. It has also been used in some countries for the management of actinic keratoses and fever. Eye drops of diclofenac sodium are used for the prevention of intra-operative miosis during cataract extraction, for the treatment of inflammation after surgery or laser treatment of the eye, for pain in corneal epithelial defects after surgery or accidental trauma, and for the relief of ocular signs and symptoms of seasonal allergic conjunctivitis.

The usual **oral** or **rectal** dose of diclofenac sodium is 75 to 150 mg daily in divided doses. In the UK the maximum dose regardless of route or indication is 150 mg daily; however, in the USA a maximum oral dose of 200 mg daily is allowed in the treatment of rheumatoid arthritis. Modified-release preparations of diclofenac sodium are available for oral use. Diclofenac has also been given in equivalent oral doses as the free acid in dispersible preparations for short-term treatment up to 3 months long. Diclofenac is also given orally as the potassium salt. Doses of the potassium salt are similar to those for diclofenac sodium. Diclofenac potassium is also used in the treatment of migraine in an initial dose of 50 mg taken at the first signs of an attack; an additional dose of 50 mg may be taken after 2 hours if symptoms persist. If necessary further doses of 50 mg may be taken every 4 to 6 hours to a maximum daily dose of 200 mg.

Diclofenac sodium may also be given by deep intramuscular **injection** into the gluteal muscle in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. Diclofenac sodium may also be given as a continuous or intermittent intravenous infusion in glucose 5% or sodium chloride 0.9% (both previously buffered with sodium bicarbonate) or as a bolus intravenous injection.. For the treatment of postoperative pain a dose of 75 mg may be given over 30 to 120 minutes or as a bolus injection. The dose may be repeated once after 4 to 6 hours if necessary. To prevent postoperative pain, an initial dose of 25 to 50 mg diclofenac sodium may be given after surgery over 15 to 60 minutes followed by 5 mg/hour to a maximum of 150 mg daily. Alternatively, the initial dose may be given as a bolus injection over 5 to 60 seconds followed by additional injections up to the maximum daily dosage; this may be repeated after 4 to 6 hours if necessary although the *total* dose should not exceed the maximum daily dose of 150 mg. The maximum period recommended for parenteral use is 2 days. Diclofenac sodium is also used intramuscularly in renal colic in a dose of 75 mg repeated once after 30 minutes if necessary.

For dosage details in children see below.

Diclofenac sodium is used as a 0.1% **ophthalmic solution** in a number of situations:

- for the prevention of intra-operative miosis during cataract surgery, it is instilled in the appropriate eye 4 times during the 2 hours before surgery
- for the treatment of postoperative inflammation after cataract surgery, it is instilled 4 times daily for up to 28 days starting 24 hours after surgery
- for the control of post-photorefractive keratectomy pain, it is instilled twice in the hour before surgery, then one drop twice at 5-minute intervals immediately after the procedure, and then every 2 to 5 hours while awake for up to 24 hours
- for pain control after accidental trauma one drop is instilled 4 times daily for up to 2 days
- in the treatment of inflammation and discomfort after strabismus surgery one drop is instilled 4 times daily for the first week; this is reduced to 3 times daily in the second week, twice daily in the third week, and as required for the fourth week
- for the control of inflammation after argon laser trabeculoplasty one drop is instilled 4 times during the 2 hours before the procedure followed by one drop 4 times daily for up to 7 days after the procedure
- for the treatment of pain and discomfort after radial keratotomy one drop is instilled before surgery followed by one drop immediately after surgery and then one drop 4 times daily for up to 2 days
- to relieve symptoms of seasonal allergic conjunctivitis one drop is instilled 4 times daily as necessary

Diclofenac diethylamine is used **topically** as a gel containing the equivalent of 1% of diclofenac sodium for the local symptomatic relief of pain and inflammation; it is applied to the affected site 3 or 4 times daily; treatment should be reviewed after 14 days or after 28 days if used for osteoarthritis. A topical solution of diclofenac sodium 1.6% is also available for the treatment of osteoarthritis in superficial joints such as the wrist or knee; it is applied in small aliquots to achieve a total of 20 or 40 drops, depending on the size of the joint, and repeated four times daily. Diclofenac is also used in the management of actinic keratoses; it is applied twice daily as diclofenac sodium gel 3% for 60 to 90 days but the optimum therapeutic effect may not be seen until 30 days after the end of treatment. Diclofenac epolamine is also used topically as a plaster containing the equivalent of 1% of diclofenac sodium for local symptomatic pain relief in ankle sprain and epicondylitis. In the treatment of ankle sprain, 1 plaster is applied once daily for a maximum of 3 days and for epicondylitis, 1 plaster is applied twice daily for a maximum of 14 days.

Diclofenac is available in combination with misoprostol (see p.2013) for patients at risk of NSAID-induced peptic ulceration.

Administration. ***IN CHILDREN.*** In children 1 to 12 years old the licensed UK *oral* or *rectal* dose of diclofenac sodium for juvenile idiopathic arthritis is 1 to 3 mg/kg daily in divided doses. In children 6 to 12 years old diclofenac sodium may also be given rectally for the treatment of acute postoperative pain, either alone or as an adjunct to opiate therapy; a usual dose is 1 to 2 mg/kg daily in divided doses for a maximum of 4 days. The *parenteral route* is not licensed for use in children although it has been used (see below).

The *BNFC* suggests slightly different doses of diclofenac sodium: in the management of rheumatic disease, including juvenile idiopathic arthritis, in children from 6 months of age, it recommends an oral dose of 3 to 5 mg/kg daily, in 2 or 3 divided doses, up to a maximum of 150 mg daily. For relief of pain and inflammation in, for example, soft-tissue disorders, the recommended oral or rectal dose in children from 6 months of age is 0.3 to 1 mg/kg given three times daily; children 2 years of age and older may be given a similar dose once or twice daily *by intravenous infusion* or *deep intramuscular (gluteal) injection* instead, for up to 2 days. Again, a maximum daily dose of 150 mg should not be exceeded.

Diclofenac potassium has also been used in children aged over 14 years for the treatment of rheumatic disease, musculoskeletal disorders, and postoperative pain; it is given in an *oral* dose of 75 to 100 mg daily in 2 to 3 divided doses.

TOPICAL. References to the use of plasters providing sustained topical release of diclofenac epolamine,[1-6] and a systematic review of the use of a topical solution of diclofenac with dimethyl sulfoxide to treat osteoarthritis.[7] The latter was found to be effective and better tolerated than oral use.

1. Galeazzi M, Marcolongo R. A placebo-controlled study of the efficacy and tolerability of a nonsteroidal anti-inflammatory drug, DHEP plaster, in inflammatory peri- and extra-articular rheumatological diseases. *Drugs Exp Clin Res* 1993; **19:** 107–15.
2. Dreiser RL, Tisne-Camus M. DHEP plasters as a topical treatment of knee osteoarthritis—a double-blind placebo-controlled study. *Drugs Exp Clin Res* 1993; **19:** 117–23.
3. Affaitati G, *et al.* Effects of topical diclofenac (DHEP plaster) on skin, subcutis and muscle pain thresholds in subjects without spontaneous pain. *Drugs Exp Clin Res* 2001; **27:** 69–76.
4. Jenoure P-J. Évaluation d'un anti-inflammatoire non stéroïdien topique dans le traitement de la douleur et de l'inflammation: exemple de Flector Tissugel 1% dispositif local bioadhésif de diclofénac épolamine. *Presse Med* 2004; **33:** 10–13.
5. Brühlmann P, *et al.* Short-term treatment with topical diclofenac epolamine plaster in patients with symptomatic knee osteoarthritis: pooled analysis of two randomised clinical studies. *Curr Med Res Opin* 2006; **22:** 2429–38.
6. Alessandri F, *et al.* Topical diclofenac patch for postoperative wound pain in laparoscopic gynecologic surgery: a randomized study. *J Minim Invasive Gynecol* 2006; **13:** 195–200.
7. Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol* 2006; **33:** 567–73.

Actinic keratoses. Diclofenac sodium 3% in hyaluronic acid gel is used[1-3] in the treatment of actinic keratoses (see Basal Cell and Squamous Cell Carcinoma, p.673), and a meta-analysis[4] found it to be of benefit, despite previous concerns that the preparation may not be significantly more effective than hyaluronic acid gel alone.[5] An open-label comparison involving 30 patients with multiple actinic keratoses suggested that 90 days of treatment with diclofenac sodium 3% gel (to lesions on one side of the face and scalp) was better tolerated, but slightly less effective, than 28 days of treatment with fluorouracil 5% cream (to lesions on the other side).[6]

1. Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. *Arch Dermatol* 1997; **133:** 1239–42.
2. Rivers JK, *et al.* Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; **146:** 94–100.
3. Ulrich C, *et al.* Treatment of multiple actinic keratoses with topical diclofenac 3% gel in organ transplant recipients: a series of six cases. *Br J Dermatol* 2007; **156** (suppl 3): 40–2.
4. Pirard D. *et al.* Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. *Arch Dermatol Res* 2005; **297:** 185–9.
5. McEwan LE, Smith JG. Topical diclofenac/hyaluronic acid gel in the treatment of solar keratoses. *Australas J Dermatol* 1997; **38:** 187–9.
6. Smith SR, *et al.* Bilateral comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% 5-fluorouracil cream in the treatment of actinic keratoses of the face and scalp. *J Drugs Dermatol* 2006; **5:** 156–9.

Pain. Reviews.

1. Barden J, *et al.* Single dose oral diclofenac for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 07/11/06).

Preparations

BP 2008: Diclofenac Gel; Gastro-resistant Diclofenac Tablets; Prolonged-release Diclofenac Capsules; Prolonged-release Diclofenac Tablets;
USP 31: Diclofenac Potassium Tablets; Diclofenac Sodium Delayed-release Tablets; Diclofenac Sodium Extended-Release Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ainedif; Aktiosan†; Aldoron NF; Algicler; Algioxib; Anaflex; Atomo Desinflamante Geldic; Banoclus; Befol; Blokium; Calmoflex; Cataflam†; Curinflam; Damixa†; Desinflam†; DFN; Diastone; Diclac; Diclogesic; Diclogrand; Diclomar; Diclonex; Difenac; Difenac Forte; Dilam; Dioxaflex; Disipan; Dolo Tomanil; Dolofenac; Doloneitor; Dolvan; Doxtran; Faboflem; Flexin; Flexiplen; Flogenac†; Flogolisin; Flotac†; Fluxpiren; Gel Antiinflamatorio†; Gentisalyl; Iglodine; Imanol; Indofeno†; Ingeclof; Klonafenac; Lenitil†; Levedad; Lorbifenac; Metaflex NF; Miocalm; Nalgiflex; Natura Fenac; Norviken; Oxa; Oxaprost; Pronix; Quer-Out; Rati Salil D; Rodinac; Salicrem Forte; Silfox; Tomanil; Vesalion; Viartril NF; Vimultisa; Virobron Gel; Virobron NF; Volforte; Voltaren; Voltaren Colirio; Voltaren Migra; Xedenol; Xina†; ***Austral.:*** Arthrotec; Clonac; Dencorub Anti-Inflammatory†; Diclac; Diclohexal; Dinac; Fenac; Imflac; Solaraze; Voltaren; Voltaren Ophtha; ***Austria:*** Agilomed; Algefit; Arthrotec; Dedolor; Deflamat; Deflamm; Diclac; Diclaxol; Diclo-B; Diclobene; Diclomelan; Diclostad; Diclosyl; Difene; Dolo-Voltaren; Dolpasse; Fenaren; Flector; Magluphen†; Rheumabene†; Tratul; Voltaren; Zymamed; ***Belg.:*** Arthrotec; Cataflam; Diclofemed; Diclotop; Docdiclofe; Flector; Motifene; Polyflam; Voltapatch; Voltaren; ***Braz.:*** Ana-Flex; Artren; Augelit†; Bel-Gel†; Benevran; Biofenac; Cataflam; Cataflex; Cataflexym; Catalgem†; Cinaflan†; Clofaren†; Clofen†; Clofenak; Clofenid; Deltaflogin; Deltaren; Desinflex†; Diclac†; Diclo P; Diclof†; Diclofen†; Diclofenax†; Diclogenom; Diclokalium†; Diclonaco; Diclonatrium†; Diclonax; Diclonil; Diclosod†; Diclosodico; Difenan†; Dioxaflex; Dnaren; Dorflan; Dorgen; Doriflan†; Fenaflan; Fenaren; Fenburil; Fisioren; Fladon; Flamalgen†; Flanakin; Flanaren; Flexamina†; Flodin Duo; Flogan; Flogesic†; Flogiren; Flogonac†; Flotac; Infladoren†; Inflamax; Kindaren; Lifaren†; Luparen†; Maxilerg; Neocoflan; Neotaflan; Neotaren; Olfen; Optamax†; Ortoflan; Poltax; Probenxil; Prodofenaco; Profenac†; Sintofenac†; Sodix; Still; Tonaflan†; Tricin†; Vendrex; Voltaflan; Voltaflex; Voltaren; Voltaren Colirio; Voltrix; ***Canad.:*** Apo-Diclo; Arthrotec; Diclotec†; Novo-Difenac; Nu-Diclo; Pennsaid; Voltaren;

Voltaren Ophtha; ***Chile:*** 3A Ofteno; Amofen; Artren; Autdol; Cataflam; Deflamat; Diclotaren; Dicogel; Dignofenac†; Elitiran; Exflam; Flector; Flotac; Lertus; Merpal; Noxiflex†; Oftic; Pirexyl; Piroflam; Pro Lertus; Sipirac; Turbogesic; Voltaren; ***Cz.:*** Almiral; Apo-Diclo; Arthrotec†; Diclofen; Dicloreum; DIKY; Dolmina; Dorosan; Feloran†; Flector; Inflamac†; Monoflam; Myogit; Naclof†; Naklofen; Olfen; Rewodina; Uniclophen; Uno; Veral; Voltaren; ***Denm.:*** Arthrotec; Diclodan; Diclogea†; Diclon; Difenet; Flector; Modifenac; Solaraze; Voltaren; Vostar; ***Fin.:*** Arthrotec; Diclometin; Diclomex; Eeze; Flector; Motifene; Solaraze; Trabona†; Voltaren; ***Fr.:*** Artotec; Flector; Solaraze; Voldal; Voltarendolo; Voltarene; Xenid; ***Ger.:*** Allvoran; Arthrotec; Benfofen†; Delphinac†; Diclac; Diclo; Diclo-Divido; Diclo-Gel; Diclo-Puren; Dicloxa-saar; Diclodoc; Diclofenbeta; Diclophlogont†; Difen; Dolgit-Diclo; duravolten†; Effekton; Jenafenac; Jutafenac; Lexobene†; Monoflam; Myogit; Rewodina; Sigafenac†; Solaraze; Voltaren; Voltaren Ophtha; ***Gr.:*** Anthraxiton; Arthrotec; Cataflam†; Clonac†; Declofon; Delimon; Denaclof; Diclofast; Diclophlogont†; Dicloplast; Difend†; Dinaclon†; Evinopon; Eyeclof; Fenoclof; Figrel†; Flefarmin; Optobet; Pengon†; Pennsaid; Relipain; Rheumavek; Ruvominox; Sfinac; Topalgon; Urigon; Vilacril†; Vilonit; Voltaren; Vurdon; ***Hong Kong:*** Almiral; Analpan; Apo-Diclo; Arthrotec; Cataflam; Clofec; Clofenac; Curinflam; Diclo-Denk; Diclofen; Diclogesic; Diclowal†; Difenac; Difenol; Erdon; Eurofenac; Flector; Flogofenac; Grofenac; Inflanac; Novo-Difenac†; Olfen; Remafen; Remethan; Ren; Rhemofenac; Uniren; Vartelon; Voltaren; Voltaren Ophtha; Votalen; Zolterol; ***Hung.:*** Cataflam; Diclac; Diclomel; Flamenil; Flector; Fortedol; Huma-Difenac†; Olfen†; Veral†; Voltaren; Voltaren Ophta; ***India:*** Cofenac; Diclomol; Diclonac; Dicloran†; Doflex; Dolocide K; Dolocide Plus; Esgipyrin DS; Fenlodac†; Fensaide†; I-Gesic; Jonac; K-Fenac; Nac; Nac Gel; Oxalgin; Oxalgin-D; Oxalgin-SR; Profenac; Reactine; Relaxyl; Solunac; Tromagesic; Tromax; Voveran; ***Indon.:*** Abdiflam; Alflam; Atranac; Berifen; Cataflam; Catanac; Deflamat; Dicloflam; Diclomec; Diflam; Divoltar; Eflagen; Exaflam; Fenaren; Fenavel; Flamar; Flamenac; Kadiflam; Kaflam; Kamaflam; Klotaren; Laflanac; Linac; Matsunaflam; Merflam; Nadifen; Neurofenac; Nichoflam; Nilaren; Potazen; Prostanac; Provoltar; Reclofen; Renadinac; Renvol; Scanaflam; Scantaren; Tirmaclo; Valto; Volmatik; Voltadex; Voltaren; Voltaren Ophtha; Voren; X-Flam; Xepathritis; Yariflam; Zegren; ***Irl.:*** Arthrotec; Cataflam; Diclac; Diclo; Diclomax; Diclomel; Difene; Solaraze; Vologen†; Voltarol; Voltarol Ophtha; ***Israel:*** Abitren; Arthrotec; Betaren; Cataflam; Dicloplast; Diclorengel; Olfen; Voltaren; Voltaren Ophtha; ***Ital.:*** Algosenac; Artrofenac†; Artrotec; Dealgic; Deflamat; Diclocular; Diclofan; Dicloftil; Dicloral; Dicloreum; Diclotears; Dolaut; Doroxan; Dropflam; Fenadol; Fender; Flector; Flogofenac; Forgenac; Itami; Leviogel; Lisiflen†; Misofenac; Molfenac; Novapirina; Pennsaid; Ribex Flu†; Solaraze; Topfans; Voltadol; Voltaren; Voltfast; Zeroflog; ***Jpn:*** Anavan; ***Malaysia:*** Almiral; Apo-Diclo†; Cataflam; Clofec; Clofenac; Difnal; Fenac; Fenadium†; Inflanac; Lesflam; Neo-Pyrazon; Olfen; Remafen†; Remethan; Rhewlin†; Taks†; Uniren; Voltaren; Voren; Wari-Diclowal†; Zolterol; ***Mex.:*** 3A Ofteno; Alsidexten; Ariflam; Artrenac; Artrenac Pro; Artrene; Artrotec; Atalak; Cataflam; Clo-Far; Clonodifen; Coral; Deflox; Dicfafena; Diclac; Dicloran; Diclosol; Dioxaflex; Dirret; Docril; Dofen; Dolaren; Dolflam; Dolofenac; Doltarac; Evadol; Fenagel; Fenalgin; Fervex; Flamydol; Flamygel; Flankol; Flogoken; Flotac; Fortical; Fustaren; Galedol; Hipo Sport; Lertus; Lifenac; Liroken; Lodyfen; Logesic†; Lonatec; Lufac-Z; Mafena; Manacon; Merxil; Metracin; Musol; Nediclon; Neo-Dolaren; Pharmaflam; Practiser; Precifenac; Selectofen; Solof; Still; Uni-Fenil†; Vicmafen; Volfenac; Voltaren; ***Neth.:*** Arthrotec; Artrotec; Cataflam; Itami; Misofenac; Naclof; Normulen; Otriflu; Voltaren; ***Norw.:*** Arthrotec; Cataflam; Modifenac; Otriflu; Solaraze; Voltaren; Voltaren Ophtha; ***NZ:*** Apo-Diclo; Cataflam; Diclax; Diclohexal; Flameril; Voltaren; Voltaren Ophtha; Voltfast; ***Philipp.:*** Acuflam; Cataflam; Clofenix; Clofil; Clonaren; Difenax; Diflapane; Doloflam; Dycon; Eslofen; Fenaspec; Lobafen; Lofenax; Neo-Pyrazon; Nepenthe; Parafortan; Rheuflam; Uniclonax; Volfenn; Voltaren; Voren; Zobid; ***Pol.:*** Apo-Diclo; Arthrotec; Cataflam; Diclac; Dicloberl; DicloDuo; Dicloratio; Dicloreum; Difadol; Diklonat P; Diklozijaja; Felogel; Majamil; Naclof; Naklofen; Olfen; Ratiogel; Rewodina; Veral; Voltaren; Voltenac; ***Port.:*** Arthrotec; Cataflam; Clofen; Dicloabak; Diclodent; Diclofital; Diclospray; Diclotec; Difnan; Dofene; Dolacen; Dorcalor; Fenac; Fenil-V; Flameril; Flector; Olfen; Otriflu; Painex; Pennsaid; Solaraze; Voltaren; ***Rus.:*** Almiral (Алмирал); Apo-Diclo (Апо-дикло); Arthrotec (Артротек)†; Diclac (Диклак); Diclo-F (Дикло-ф); Diclobene (Диклобене); Dicloberl (Диклоберл); Diclonat (Диклонат); Dicloran (Диклоран); Diclovit (Дикловит); Feloran (Фелоран)†; Naclof (Наклоф); Naklofen (Наклофен); Naklofen Duo (Наклофен Дуо); Rapten Rapid (Рапттен Рапид); Voltaren (Вольтарен); ***S.Afr.:*** Adco-Clofelam; Arcanafenac; Arthrotec; Arthru-Derm; Cataflam; Dicloflam; Diclohexal; Dynak; Flexagen; Fortfen; Infla-Ban; K-Fenak; Panamor; Pharmaflam†; Veltex; Voltaren; Voltaren Ophtha; ***Singapore:*** Almiral; Cataflam; Clofec; Clofenac; Diclo; Diclo-Denk†; Dicloran; Diclowal†; Difenac; Difnal; Inac; Inflanac; Lesflam; Neo-Pyrazon†; Olfen; Pritaren; Remafen; Remethan†; Rhewlin; Ultrafen; Uniren; Voltaren; Voltaren Ophtha; Voren; Zolterol; ***Spain:*** Artrotec; Di Retard; Dolo Nervobion; Dolo-Voltaren; Dolotren; Luase; Normulen; Sulexon; Voltaren; ***Swed.:*** Arthrotec; Flector; Modifenac†; Solaraze; Voltaren; Voltaren Ophtha; Voltaren T; ***Switz.:*** Agofenac†; Arthrotec; Athrofen; Deflamat†; Diclac; diclo-basan; Diclo†; Diclosifar; Ecofenac; Effigel; Flector; Fortenac; Grofenac; Inflamac; Olfen; Primofenac; Relova; Tonopan; Vifenac; Voltaren Dolo; Voltaren Emulgel; Voltaren Ophta; Voltarene; ***Thai.:*** Almiral†; Ammi-Votara; Ammimac; Arclonac; Arthrotec†; Cataflam; Catanac; Cencenag; Chinclonac; Clofec; Clofon; Demac; Diclofen†; Diclogel; Diclolan; Diclomol; Diclosian; Difelene†; Difen; Difenac; Difengesic; Difeno; Dinac; Dinefec†; Dosanac; Fenac; Fenagel; Flexy; Inflanac; Lesflam; Lofenac; Masaren; Medaren†; Myfenax; Myonac; N-Zen; Naclof; Olfen†; Ostaren; Posnac; Putaren†; Remethan; Rhumanol; Rumatab†; Sefnac; Silflam†; Subsyde; Taks; Tarjen†; Tarjena; Uniren; Vasalen; Veenac; Ventarone; Volfenac; Volnac; Volta; Voltanac; Voltaren; Volverac; Votamed; ***Turk.:*** Actinoma; Cataflam; Deflamat; Diclo-flam; Diclomec; Difenak; Dikloron; Dolorex; Inflased; Kalidren; Miyadren; Voltaren; Voltaren Ophta; ***UAE:*** Clofen; ***UK:*** Acoflam†; Arthrotec; Defanac; Defenac; Dexomon; Dicloflex; Diclomax; Diclovol; Diclozip; Dyloject; Econac; Fenactol; Flamatak; Flamrase; Lofensaid†; Motifene; Pennsaid; Rheumatac; Rhumalgan; Slofenac; Solaraze; Volraman; Volsaid; Voltarol; Voltarol Ophtha; ***USA:*** Arthrotec; Cataflam; Flector; Solaraze; Voltaren; ***Venez.:*** 3A Ofteno; Arthrotec; Artren; Campal; Cataflam; Clofen; Clofenac; Diagesic; Diclofen P; Diclosal; Diclostan†; Difenac; Diklason; Diralon; Dival; Doltren†; Flogaren; Flotac; Klafenac; Viavox; Voltaren; Volten; Votaxil.

Multi-ingredient: ***Arg.:*** Albesine Biotic; Algicler; Algio Nervomax; Algio Nervomax Fuerte; Amixen Plus; Befol Plus; Belmalen; Blokium B12; Blokium Flex; Blokium Gesic; Corteroid Gesic; Curinflam Plus; Delta Tomanil B12; Desinflam Biotic†; Diclogesic Forte; Diclogesic Plus B12; Diclogesic Relax; Diclomar Flex; Diclonex Relax; Dioxaflex B12; Dioxaflex Forte; Dioxaflex Gesic; Dioxaflex Plus; Dolo Nervobion; Dolo Nervobion 10000; Dolvan Flex; Doxtran B12; Doxtran Flex; Doxtran Gesic; Flaval; Glifapen; Hyanac†; Iglodine Flex; Ingebrax; Lertus Biotic†; Metaflex Gesic; Metaflex Plus NF; Meticil; Mio Aldoron NF; Mio-Virobron NF; Nalgiflex Relax; Oxa B12; Oxa Forte; Oxa Sport; Oxadisten; Oxafem; Oxagesic; Pancloflex; Panclogesic; Rodinac B12; Rodinac Biotic; Rodinac Flex; Rodinac Gesic; Silfox Flex; Tafirol Artro; Tobradiclo; Tobratlas; Tomanil Flex; Vesalion B12; Vesalion Flex; Vesalion Gesic; Viartril Flex; Virobron B12 NF; Voltaren Flex; Voltaren Forte; Xedenol B12; Xedenol Flex; Xedenol Gesic; ***Austria:*** Diclovit; Dolo-Neurobion; Neodolpasse; Neurofenac; Voltamicin; ***Belg.:*** Ocubrax; ***Braz.:*** Algi-Butazolon†; Algi-Tanderil†; Beserol; Cedrilax†; Codaten; Diclofetamol; Flexalgin; Mioflex A; Sedilax; Tandene; Tanderalgin; Tandriflan; Tandrilax; Torsilax; Trilax†; ***Cz.:*** Neodolpasse; Voltamicin†; ***Ger.:*** Combaren; Voltaren Plus; ***Gr.:*** Tobrafen; ***Hong Kong:*** Neurofenac†; Vartelon-B; Vidaclofen-Plus; ***Hung.:*** Neodolpasse; Ocubrax†; Voltamicin†; ***India:*** Actimol; Buta-Proxyvon; Cip-Zox; Cipzen D; Cofenac; Diclogenta; Diclomol; Dicloran MS; Dicloran-A†; Diclospa; Diser; Doflex Plus; Dolocide KP; Dolocide MR; DP Gesic; Duoflam Gel; Esgipyrin; Fenaplus; Fenaplus-MR; Fensaide-P†; Flamar-MX; Flanzen-D; Inflazone; Myospaz Forte; New Panazox; Nicip D; Omnigel; Osteoflam-MR; Oxalgin-DP; Pacizox; Paracip Plus; Parvon Forte; Reactine Forte; Reactine Plus; Relaxyl Plus; Spasmo-Proxyvon Forte; Systaflam; ***Indon.:*** Dolofenac; ***Ital.:*** Voltamicin†; ***Malaysia:*** Voren Plus; ***Mex.:*** Ariflam Forte; Diclovith-B; Dolaren; Dolo-Neurobion; Dolo-Pangavit; Duciclon; Duoflex; Empatil; Lertus CD; Ortocol; Tafirol AC; Trazinac; Tribedoce Compuesto; Uni-Dox; Voltaren Forte; ***Pol.:*** Venozel; ***Rus.:*** Diclofenacol (Диклофенакол); Dicloran Plus (Диклоран Плюс); ***Singapore:*** Voltamicin†; ***Spain:*** Ocubrax; ***Switz.:*** Tobrafen; Voltamicin; ***Turk.:*** Ocubrax; ***Venez.:*** Combaren; Painfort; Todenac; Trazinac.

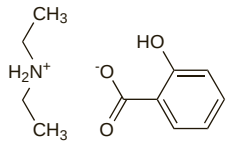
Diethylamine Salicylate

Diaethylamini Salicylas; Dietylaminsalicylat; Dietyyliamiinisalisylaatti; Salicilato de dietilamina; Salisilat Dietilamin.

Диэтиламин Салицилат; Салицилат Диэтиламина

$C_{11}H_{17}NO_3$ = 211.3.

CAS — 4419-92-5.



Pharmacopoeias. In *Br.* and *Chin.*

BP 2008 (Diethylamine Salicylate). White or almost white, odourless or almost odourless crystals. Very soluble in water; freely soluble in alcohol and in chloroform. Protect from light. Avoid contact with iron or iron salts.

Profile

Diethylamine salicylate is a salicylic acid derivative used topically in rubefacient preparations similarly to methyl salicylate (p.85) for rheumatic and muscular pain.

Preparations

BP 2008: Diethylamine Salicylate Cream.

Proprietary Preparations (details are given in Part 3)

Belg.: Algesal; ***Canad.:*** Physiogesic; ***Fin.:*** Algesal; ***Hung.:*** Aciphen; ***India:*** Multigesic†; ***Ital.:*** Algesal†; ***Neth.:*** Algesal; ***Norw.:*** Algesal; ***Pol.:*** Saldiam; ***Port.:*** Algicum; Algiderma; Massagim; ***Swed.:*** Algesal; ***Turk.:*** Algesal; Reparil N; ***UK:*** Algesal; Lloyd's Cream; ***Venez.:*** Alesal.

Multi-ingredient: ***Arg.:*** Algesal; Cartiflex; Crema Antiinflamatoria; Feparil†; Rati Salil Flex; Salicrem; ***Austral.:*** Rubesal; ***Austria:*** Algesal; Derivon; Dolo-Menthoneurin; Dolorex†; Igitur-antirheumatische; Igitur-Rheumafluid; Latesyl; Pasta rubra salicylata; Reparil; Rheugesal; Thermal; ***Belg.:*** Reparil; ***Braz.:*** Reparil; ***Chile:*** Repariven; ***Cz.:*** Algesal; Reparil-Gel N; ***Fr.:*** Algesal Suractive; Reparil; Traumalgyl; ***Ger.:*** Algesal; Algesalona†; Dolo-Menthoneurin†; Doloneuro†; Reparil-Gel N; ***Gr.:*** Algesal Suractive; Ponostop; ***Hong Kong:*** Reparil; Rubesal; ***Hung.:*** Algesal; Reparil N; ***Indon.:*** Algesal Superactive; ***Ital.:*** Edeven; Reparil; Sedalpan; Via Mal Traumagel; ***Mex.:*** Algesal†; ***Neth.:*** Algesal Forte; ***Norw.:*** Thermal†; ***Pol.:*** Reparil N; ***Port.:*** Algesal; Latesil; Medalginan; Venoparil; ***S.Afr.:*** Reparil; ***Spain:*** Algesal; Contusin; Doctomitil†; Dolmitin; Feparil; Radio Salil; ***Switz.:*** Algesal†; Algesalona†; Mavena Proctal-Gen; Reparil; ***Thai.:*** Reparil; Veno Gel; ***Turk.:*** Algesal Suractive; Prepagel; ***UAE:*** Rubicalm; ***UK:*** Fiery Jack; Transvasin Heat Spray; ***Venez.:*** Lemazol.

Diflunisal *(BAN, USAN, rINN)*

Diflunisaali; Diflunisalis; Diflunisalum; Difluniszal; MK-647. 5-(2,4-Difluorophenyl)salicylic acid.

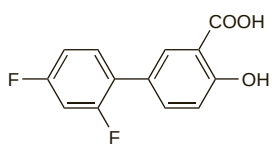
Дифлунисал

$C_{13}H_8F_2O_3$ = 250.2.

CAS — 22494-42-4.

ATC — N02BA11.

ATC Vet — QN02BA11.



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

Ph. Eur. 6.2 (Diflunisal). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Diflunisal). A white to off-white, practically odourless, powder. Insoluble in water and in hexane; freely soluble in alcohol and in methyl alcohol; soluble in acetone and in ethyl acetate; slightly soluble in carbon tetrachloride, in chloroform, and in dichloromethane.

Adverse Effects and Treatment

As for NSAIDs in general, p.96. The commonest adverse effects occurring with diflunisal are gastrointestinal disturbances, headache, and rash. Peptic ulceration and gastrointestinal bleeding have been reported. Dizziness, drowsiness, insomnia, and tinnitus may also occur.

Effects on the blood. Haematological adverse effects associated with diflunisal appear to be infrequent. Thrombocytopenia associated with diflunisal-induced peripheral platelet destruction has been reported in a patient with rheumatoid arthritis.[1] Heinz-body haemolytic anaemia has also been reported, see Hypersensitivity, below.

1. Bobrove AM. Diflunisal-associated thrombocytopenia in a patient with rheumatoid arthritis. *Arthritis Rheum* 1988; **31:** 148–9.

Effects on the kidneys. Acute interstitial nephritis, presenting as acute oliguric renal failure, erythroderma, and eosinophilia has followed the use of diflunisal.[1]

1. Chan LK, *et al.* Acute interstitial nephritis and erythroderma associated with diflunisal. *BMJ* 1980; **280:** 84–5.

Effects on the lungs. For reference to pneumonitis associated with diflunisal therapy, see Hypersensitivity, below.

Effects on the skin. Reports of Stevens-Johnson syndrome associated with diflunisal.[1,2] See also Hypersensitivity, below.

1. Hunter JA, *et al.* Diflunisal and Stevens-Johnson syndrome. *BMJ* 1978; **2:** 1088.
2. Grom JA, *et al.* Diflunisal-induced erythema multiforme major. *Hosp Formul* 1986; **21:** 353–4.

Hypersensitivity. Three cases of hypersensitivity to diflunisal in which the main clinical features were fever, elevated liver enzyme values, erythroderma, and eosinophilia, have been reported.[1] Heinz-body haemolytic anaemia occurred in one of the patients. Other hypersensitivity reactions associated with diflunisal therapy have included pneumonitis[2] and fulminant necrotising fasciitis.[3]

1. Cook DJ, *et al.* Three cases of diflunisal hypersensitivity. *Can Med Assoc J* 1988; **138:** 1029–30.
2. Rich MW, Thomas RA. A case of eosinophilic pneumonia and vasculitis induced by diflunisal. *Chest* 1997; **111:** 1767–9.
3. Krige JEJ, *et al.* Necrotising fasciitis after diflunisal for minor injury. *Lancet* 1985; **ii:** 1432–3.

Overdosage. Diflunisal poisoning has sometimes been fatal.[1,2] A dose of 15 g has been reported to have caused death when no other drugs were involved but a dose of 7.5 g has also been fatal when taken with other drugs.

1. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 1–21.
2. Levine B, *et al.* Diflunisal related fatality: a case report. *Forensic Sci Int* 1987; **35:** 45–50.

Precautions

As for NSAIDs in general, p.98. Diflunisal may need to be given in reduced dosage in patients with significant renal impairment and should not be given when renal impairment is severe. Aspirin and other acetylated salicylates are not recommended for use in children unless specifically indicated, because of the risk of Reye's syndrome. Although this precaution has not been specifically extended to diflunisal it is not generally licensed for use in children.

Interactions

For interactions associated with NSAIDs, see p.99.

Aspirin may produce a small decrease in the plasma concentration of diflunisal. Diflunisal has been reported to increase the plasma concentrations of indometacin and paracetamol; diflunisal with indometacin has been associated with fatal gastrointestinal haemorrhage and therefore the combination should not be used. Regular use of antacids may reduce the absorption of diflunisal.

Benzodiazepines. For the effect of diflunisal on plasma concentrations of *oxazepam*, see p.989.

Probenecid. Average steady-state plasma concentrations of diflunisal were increased by 65% when it was given with probenecid.[1] This was due mainly to reduced formation of the phenolic and acyl glucuronides. However, plasma concentrations of these glucuronides and the sulfate conjugate were also increased even more because probenecid also reduced their renal clearance.

1. Macdonald JI, *et al.* Effect of probenecid on the formation and elimination kinetics of the sulphate and glucuronide conjugates of diflunisal. *Eur J Clin Pharmacol* 1995; **47:** 519–23.

Pharmacokinetics

Diflunisal is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 to 3 hours after ingestion of a single dose. It is more than 99% bound to plasma protein and has a plasma half-life of about 8 to 12 hours. Diflunisal exhibits non-linear pharmacokinetics so that doubling the dose more than doubles drug accumulation. Due to the long half-life and non-linear kinetics, several days are required to reach steady-state plasma concentrations after multiple dosing. The time to steady-state concentrations can be reduced by giving an initial loading dose. Concentrations of diflunisal in synovial fluid reach about 70% of those in plasma. Diflunisal is excreted in the urine mainly as glucuronide conjugates. Some biliary recycling may