added. Freely soluble in water and in alcohol; very soluble in dichloromethane. Protect from light.

Dependence and Withdrawal
As for Opioid Analgesics in general, p.101.

Adverse Effects, Treatment, and Precautions
As for Opioid Analgesics in general, p.102.

Overdosage. Cyanosis, respiratory depression, and seizures developed in a 28-year-old woman after an overdose of a combination preparation of tilidine and naloxone.[1] The authors commented that the amount of naloxone included in the preparation, in order to prevent abuse, was insufficient to prevent respiratory depression after severe overdose.

1. Regenthal R, *et al*. Poisoning with tilidine and naloxone: toxicokinetic and clinical observations. *Hum Exp Toxicol* 1998; **17:** 593–7.

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

Interactions
For interactions associated with opioid analgesics, see p.103.

Pharmacokinetics
Tilidine is absorbed from the gastrointestinal tract. It is metabolised and excreted in the urine mainly as metabolites nortilidine (nortilidate) and bisnortilidine (bisnortilidate). Nortilidine is responsible for the analgesic activity of tilidine.

◊ References.

1. Vollmer K-O, *et al*. Pharmacokinetics of tilidine and metabolites in man. *Arzneimittelforschung* 1989; **39:** 1283–8.
2. Seiler K-U, *et al*. Pharmacokinetics of tilidine in terminal renal failure. *J Clin Pharmacol* 2001; **41:** 79–84.
3. Hajda JP, *et al*. Sequential first-pass metabolism of nortilidine: the active metabolite of the synthetic opioid drug tilidine. *J Clin Pharmacol* 2002; **42:** 1257–61.
4. Brennscheidt U, *et al*. Pharmacokinetics of tilidine and naloxone in patients with severe hepatic impairment. *Arzneimittelforschung* 2007; **57:** 106–11.

Uses and Administration
Tilidine hydrochloride is an opioid analgesic (p.104). It is used in the control of moderate to severe pain.

Tilidine hydrochloride may be given in usual oral doses of up to 50 mg four times daily. It has been given as a suppository, or by intravenous, intramuscular, or subcutaneous injection. Tilidine has also been given as the phosphate in modified release tablets. As a deterrent to abuse combined oral preparations of tilidine hydrochloride with naloxone hydrochloride are available in some countries.

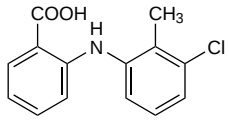
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Tinalox; Valoron†; Valtran; ***Cz.:*** Valoron†; ***Ger.:*** Andolor; Celldolor; Findol N†; Gruntin Tropfen†; Nalidin; Tili Comp; Tili-Puren; Tili†; Tilicomp; Tilidalor†; Tilidin comp; Tilidin N; Tilidin plus; Tilidin-saar; Tilidura; Tiligetic†; Tilimerck†; Tilnalox; Valoron N; ***S.Afr.:*** Valoron; ***Switz.:*** Valoron.

Tolfenamic Acid *(BAN, rINN)*

Acide Tolfénamique; Ácido tolfenámico; Acidum tolfenamicum; Kyselina tolfenamová; Tolfenaamihappo; Tolfenaminsav; Tolfenamo rūgštis; Tolfenamsyra. *N*-(3-Chloro-*o*-tolyl)anthranilic acid.

Толфенамовая Кислота

$C_{14}H_{12}ClNO_2$ = 261.7.
CAS — 13710-19-5.
ATC — M01AG02.
ATC Vet — QM01AG02.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Tolfenamic Acid). A white or slightly yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in dichloromethane; soluble in dimethylformamide. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

Adverse Effects, Treatment, and Precautions
As for NSAIDs in general, p.96.

Dysuria, most commonly in males and probably due to local irritation of the urethra by a metabolite, has been reported. Tremor, euphoria, and fatigue have also occurred. Tolfenamic acid is contra-indicated in patients with significant hepatic or renal impairment.

Breast feeding. Although tolfenamic acid is distributed into breast milk, the amount is considered by the *BNF* and licensed product information to be too small to be harmful to a breast-fed infant.

Effects on the lungs. Pulmonary infiltration has been associated with tolfenamic acid treatment in 6 patients.[1]

1. Strömberg C, *et al*. Pulmonary infiltrations induced by tolfenamic acid. *Lancet* 1987; **ii:** 685.

Interactions
For interactions associated with NSAIDs, see p.99.

Pharmacokinetics
Tolfenamic acid is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are reached about 60 to 90 minutes after an oral dose. Tolfenamic acid is about 99% bound to plasma proteins. The plasma half-life is about 2 hours. Tolfenamic acid is metabolised in the liver; the metabolites and unchanged drug are conjugated with glucuronic acid. About 90% of an ingested dose is excreted in the urine and the remainder in the faeces. Tolfenamic acid is distributed into breast milk.

Uses and Administration
Tolfenamic acid, an anthranilic acid derivative related to mefenamic acid (p.80), is an NSAID (p.99). In the treatment of acute attacks of migraine tolfenamic acid is given in a usual oral dose of 200 mg when the first symptoms appear; if a satisfactory response is not obtained this dose may be repeated once after 1 to 2 hours. Tolfenamic acid has also been given for the relief of mild to moderate pain in disorders such as dysmenorrhoea, rheumatoid arthritis, or osteoarthritis in doses of 100 to 200 mg three times daily.

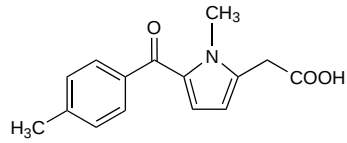
Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Flocur; ***Austria:*** Migea; ***Braz.:*** Fenamic†; ***Cz.:*** Migea; ***Denm.:*** Clotam†; Migea; ***Fin.:*** Clotam; Migea†; ***Gr.:*** Clotam; Gantil; Polmonin; Primactam; Purfalox; Tolfamic; Turbaund; ***Mex.:*** Bifenac†; Flocur†; ***Neth.:*** Clotam; Rociclyn†; ***Norw.:*** Migea†; ***Pol.:*** Migea; ***Swed.:*** Migea†; ***Switz.:*** Clotam†; ***UK:*** Clotam; ***Venez.:*** Clotan†.

Tolmetin Sodium *(BANM, USAN, rINNM)*

McN-2559-21-98; McN-2559 (tolmetin); Natrii Tolmetinum; Tolmetina sódica; Tolmétine Sodique. Sodium (1-methyl-5-*p*-toluoylpyrrol-2-yl)acetate dihydrate.

Натрий Тольметин

$C_{15}H_{14}NNaO_3,2H_2O$ = 315.3.
CAS — 26171-23-3 (tolmetin); 35711-34-3 (anhydrous tolmetin sodium); 64490-92-2 (tolmetin sodium dihydrate).
ATC — M01AB03; M02AA21.
ATC Vet — QM01AB03; QM02AA21.



(tolmetin)

Pharmacopoeias. In *US*.
USP 31 (Tolmetin Sodium). A light yellow to light orange crystalline powder. Freely soluble in water and in methyl alcohol; slightly soluble in alcohol; very slightly soluble in chloroform.

Adverse Effects, Treatment, and Precautions
As for NSAIDs in general, p.96.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were given tolmetin, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding. However, licensed product information recommends that tolmetin should be avoided in nursing mothers.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*.; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 08/11/07)

Effects on the blood. Case reports of agranulocytosis[1] and thrombocytopenia[2] associated with tolmetin.

1. Sakai J, Joseph MW. Tolmetin and agranulocytosis. *N Engl J Med* 1978; **298:** 1203.
2. Lockhart JM. Tolmetin-induced thrombocytopenia. *Arthritis Rheum* 1982; **25:** 1144–5.

Effects on the CNS. See Hypersensitivity, below.

Effects on the gastrointestinal tract. Erosive oesophagitis has been reported[1] in an 11-year-old child after ingestion of a dose of tolmetin while lying down and without drinking any water.

1. Palop V, *et al*. Tolmetin-induced esophageal ulceration. *Ann Pharmacother* 1997; **31:** 929.

Effects on the kidneys. Interstitial nephritis[1] and nephrotic syndrome[2,3] have been reported in patients given tolmetin.

1. Katz SM, *et al*. Tolmetin: association with reversible renal failure and acute interstitial nephritis. *JAMA* 1981; **246:** 243–5.
2. Chatterjee GP. Nephrotic syndrome induced by tolmetin. *JAMA* 1981; **246:** 1589.
3. Tietjen DP. Recurrence and specificity of nephrotic syndrome due to tolmetin. *Am J Med* 1989; **87:** 354–5.

Hypersensitivity. Anaphylactic shock,[1] urticaria and angioedema,[2] and aseptic meningitis[3] are among the hypersensitivity reactions reported in patients taking tolmetin.

1. Rossi AC, Knapp DE. Tolmetin-induced anaphylactoid reactions. *N Engl J Med* 1982; **307:** 499–500.
2. Ponte CD, Wisman R. Tolmetin-induced urticaria/angioedema. *Drug Intell Clin Pharm* 1985; **19:** 479–80.
3. Ruppert GB, Barth WF. Tolmetin-induced aseptic meningitis. *JAMA* 1981; **245:** 67–8.

Interactions
For interactions associated with NSAIDs, see p.99.

Pharmacokinetics
Tolmetin is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are attained about 30 to 60 minutes after ingestion. It is extensively bound to plasma proteins (over 99%) and has a biphasic plasma half-life of about 1 to 2 hours and 5 hours, respectively. Tolmetin penetrates synovial fluid and very small amounts are distributed into breast milk. It is excreted in the urine as an inactive dicarboxylic acid metabolite and its glucuronide and as tolmetin glucuronide with small amounts of unchanged drug.

Uses and Administration
Tolmetin sodium is an NSAID (p.99). It is used in musculoskeletal and joint disorders such as osteoarthritis and rheumatoid arthritis, including juvenile idiopathic arthritis. It is given orally as the sodium salt although doses are expressed in terms of the base; tolmetin sodium dihydrate 122.5 mg is equivalent to about 100 mg of tolmetin.

For the treatment of rheumatoid arthritis and osteoarthritis, the usual initial oral dose is the equivalent of 400 mg of tolmetin three times daily. Doses should be adjusted after 1 to 2 weeks according to response; maintenance doses of 600 mg to a maximum of 1800 mg daily in divided doses have been used.

For dosage details in children, see below.

Tolmetin as the free acid has been applied as a topical gel.

Administration in children. For the treatment of juvenile idiopathic arthritis in children aged 2 years and over, tolmetin sodium is given in initial oral doses equivalent to 20 mg/kg of tolmetin daily in three or four divided doses; maintenance doses of 15 mg/kg to a maximum of 30 mg/kg daily have been used.

Preparations
USP 31: Tolmetin Sodium Capsules; Tolmetin Sodium Tablets.
Proprietary Preparations (details are given in Part 3)
Austria: Tolectin†; ***Canad.:*** Tolectin†; ***Mex.:*** Tolectin; ***S.Afr.:*** Tolectin; ***Spain:*** Artrocaptin; ***Switz.:*** Tolectin†; ***Turk.:*** Tolectin; ***USA:*** Tolectin.

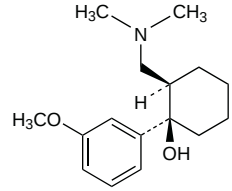
Tramadol Hydrochloride

(BANM, USAN, rINNM)

CG-315; CG-315E; Hidrocloruro de tramadol; Tramadol, chlorhydrate de; Tramadol Hidroklorür; Tramadol-hidroklorid; Tramadol-hydrochlorid; Tramadolhydroklorid; Tramadoli hydrochloridum; Tramadolihydrokloridi; Tramadolio hidrochloridas; U-26225A. (±)-*trans*-2-Dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride.

Трамадола Гидрохлорид

$C_{16}H_{25}NO_2,HCl$ = 299.8.
CAS — 27203-92-5 (tramadol); 22204-88-2 (tramadol hydrochloride); 36282-47-0 (tramadol hydrochloride).
ATC — N02AX02.
ATC Vet — QN02AX02.



(tramadol)

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Tramadol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in acetone. Protect from light.

Incompatibility. Some manufacturers state that tramadol hydrochloride injection 50 mg/mL is incompatible with injections of diazepam, diclofenac sodium, flunitrazepam, glyceryl trinitrate, indometacin, midazolam, piroxicam, and phenylbutazone if mixed in the same syringe. A study[1] also found tramadol hydrochloride injection (diluted to 400 micrograms/mL) to be incompatible with aciclovir and clindamycin when mixed together.

1. Abanmy NO, *et al.* Compatibility of tramadol hydrochloride injection with selected drugs and solutions. *Am J Health-Syst Pharm* 2005; **62:** 1299–1302.

Stability. Oral suspensions of tramadol hydrochloride 5 mg/mL, prepared by mixing crushed tablets with a strawberry syrup and *Ora-Plus* (1:1) or with *Ora-Sweet* and *Ora-Plus* (1:1) were found to be stable for at least 90 days when stored either in the refrigerator or at room temperature.[1] Oral suspensions containing tramadol hydrochloride 7.5 mg/mL and paracetamol 65 mg/mL, prepared by mixing the crushed tablets of a combination preparation with the above vehicles, were also found to be stable for at least 90 days when stored under similar conditions.[2]

1. Wagner DS, *et al.* Stability of oral liquid preparations of tramadol in strawberry syrup and a sugar-free vehicle. *Am J Health-Syst Pharm* 2003; **60:** 1268–70.
2. Johnson CE, *et al.* Stability of tramadol hydrochloride–acetaminophen (Ultracet) in strawberry syrup and in a sugar-free vehicle. *Am J Health-Syst Pharm* 2004; **61:** 54–7.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Tramadol may have lower potential for producing dependence than morphine.

◊ A WHO expert committee[1] considered in 2003 that the available information on tramadol was not sufficient to warrant international control. Studies in *animals* indicated that tramadol produced little tolerance, had mild withdrawal symptoms, and a lower abuse potential than codeine and pentazocine. Subsequently, when reviewed in 2006, the committee[2] considered that, despite an increase in its use, tramadol continued to show a low level of abuse and concluded that there was not sufficient evidence to justify a further review.

Nevertheless, there have been reports[3-8] of dependence and abuse, particularly in opioid-dependent persons, and of withdrawal symptoms. In October 1996, the UK CSM[9] commented that since June 1994 they had received reports of drug dependence in 5 patients and withdrawal symptoms associated with tramadol in 28 patients, which corresponded to a reporting rate of about 1 in 6000. Doses in excess of the recommended maximum of 400 mg daily had been taken by 5 of the patients. The duration of treatment before onset of these effects ranged from 10 to 409 days (average 3 months). Withdrawal symptoms reported were typically those of opioid withdrawal in general. A more recent report from the Swedish Medical Products Agency[10] stated that between 1996 to 2005 they had received 71 reports of withdrawal symptoms associated with tramadol; treatment duration ranged from 1 week to over 3 years at daily doses of between 50 mg to 2 g.

1. WHO. WHO expert committee on drug dependence: thirty-third report. *WHO Tech Rep Ser 915* 2003. Also available at: http://libdoc.who.int/trs/WHO_TRS_915.pdf (accessed 26/06/08)
2. WHO. WHO expert committee on drug dependence: thirty-forth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
3. Rodriguez Villamañan JC, *et al.* Withdrawal syndrome after long-term treatment with tramadol. *Br J Gen Pract* 2000; **50:** 406.
4. Yates WR, *et al.* Tramadol dependence with no history of substance abuse. *Am J Psychiatry* 2001; **158:** 964.
5. Brinker A, *et al.* Abuse, dependence, or withdrawal associated with tramadol. *Am J Psychiatry* 2002; **159:** 881.
6. Skipper GE, *et al.* Tramadol abuse and dependence among physicians. *JAMA* 2004; **292:** 1818–19.
7. Soyka M, *et al.* Tramadol use and dependence in chronic noncancer pain patients. *Pharmacopsychiatry* 2004; **37:** 191–2.
8. Ripamonti C, *et al.* Withdrawal syndrome after delayed tramadol intake. *Am J Psychiatry* 2004; **161:** 2326–7.
9. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; **22:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
10. Läkemedelsverket (Medical Products Agency—Sweden). Utsättningsreaktioner av tramadol—ett större problem än förväntat? (issued 14 November, 2006). Available at: http://www.lakemedelsverket.se/Tpl/NewsPage____5449.aspx (accessed 26/06/08)

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Tramadol may produce fewer typical opioid adverse effects such as respiratory depression and constipation. In addition to hypotension, hypertension has occasionally occurred.

Effects on the CNS. The UK CSM[1] commented in February 1995 that since June 1994 they had received reports of 15 patients who had experienced *confusion* and/or *hallucinations* while taking tramadol. The majority of the reactions developed 1 to 7 days after starting treatment and in most patients resolved rapidly on withdrawal. It was noted that psychiatric reactions comprised about 10% of all reactions reported with tramadol.

In a later comment[2] in October 1996, the CSM noted that 27 reports of *convulsions* and one of worsening epilepsy had been received, which corresponded to a reporting rate of about 1 in 7000. Of the 5 patients receiving intravenous tramadol, 2 had been given doses equivalent to 1.45 and 4 g daily, well in excess of those recommended (see also Overdosage, below). Of the patients receiving oral tramadol, the majority were taking other drugs known to cause convulsions, including tricyclic antidepressants and SSRIs. A similar pattern has been reported in the USA[3] and Australia.[4-6]

A debilitating CNS-mediated reaction to an initial dose of tramadol has been described in a patient.[7] Symptoms, which lasted about 4 hours, included ataxia, dilatation of the pupils, numbness in all limbs, tremulousness, and dysphoria. Although the exact mechanism of the reaction was not known, it was suggested that since the patient was an extensive metaboliser with very high activity of the cytochrome P450 isoenzyme CYP2D6, high concentrations of the active *O*-desmethyl metabolite were the cause. The patient recovered with no sequelae. It is possible that this represents a case of the *serotonin syndrome*, since tramadol is known to be associated with this condition, particularly at high doses or when given with other drugs that raise serotonin concentrations.[4]

1. CSM/MCA. Tramadol (Zydol)—psychiatric reactions. *Current Problems* 1995; **21:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015618&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
2. CSM/MCA. Tramadol—(Zydol, Tramake and Zamadol). *Current Problems* 1996; **22:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023218&RevisionSelectionMethod=LatestReleased (accessed 26/06/08)
3. Kahn LH, *et al.* Seizures reported with tramadol. *JAMA* 1997; **278:** 1661.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Tramadol—four years experience. *Aust Adverse Drug React Bull* 2003; **22**: 1–2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0302.pdf (accessed 26/06/08)
5. Labate A, *et al.* Tramadol and new-onset seizures. *Med J Aust* 2005; **182:** 42–3.
6. Boyd IW. Tramadol and seizures. *Med J Aust* 2005; **182:** 595–6.
7. Gleason PP, *et al.* Debilitating reaction following the initial dose of tramadol. *Ann Pharmacother* 1997; **31:** 1150–2.

Effects on the respiratory system. Respiratory depression has been reported after tramadol infusion anaesthesia,[1] although in a postoperative study[2] tramadol had no significant respiratory depressant effect when equianalgesic doses of morphine, pentazocine, pethidine, piritramide, and tramadol were compared.

1. Paravicini D, *et al.* Tramadol-infusionsanaesthesie mit Substitution von Enfluran und differenten Lachgaskonzentrationen. *Anaesthesist* 1985; **34:** 20–7.
2. Fechner R, *et al.* Clinical investigations on the effect of morphine, pentazocine, pethidine, piritramide and tramadol on respiration. *Anasth Intensivmed* 1985; **26:** 126–32.

Overdosage. In a multicentre case series,[1] 126 cases of tramadol toxicity were reported between October 1995 and August 1996; of these, 87 involved exposure to tramadol alone. Common symptoms included lethargy, nausea, tachycardia, and agitation; seizures were also noted. Respiratory depression was seen in only 2 patients. The inhibitory effects of tramadol on monoamine reuptake, rather than its opioid effects, was considered to result in much of its toxicity. A similar pattern of toxicity has also been seen in a more recent report.[2] In 190 tramadol-only exposures reported between January 1999 and July 2001, the main symptoms of overdosage were CNS depression, nausea and vomiting, tachycardia, and seizures. Again, the incidence of respiratory depression was rare, with only 1 case reported.

1. Spiller HA, *et al.* Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol* 1997; **35:** 361–4.
2. Marquardt KA, *et al.* Tramadol exposures reported to statewide poison control system. *Ann Pharmacother* 2005; **39:** 1039–44.

Precautions

As for Opioid Analgesics in general, p.103.

Tramadol should be used with caution in patients with renal or hepatic impairment and should be avoided if renal impairment is severe. Removal by haemodialysis is reported to be minimal at 7%.

Tramadol should be used with care in patients with a history of epilepsy or those susceptible to seizures. See also Effects on the CNS under Adverse Effects, above.

Abuse. See under Dependence and Withdrawal, above.

Anaesthesia. Licensed product information warns against using tramadol during very light planes of general anaesthesia because of possible intra-operative awareness, although it may be used intra-operatively provided anaesthesia is maintained with a potent volatile or intravenous anaesthetic. Intra-operative awareness was reported in 65% of a group of 20 patients when used to provide analgesia during light general anaesthesia with nitrous oxide and intermittent enflurane.[1] However, in a study[2] of 51 patients given tramadol during stable light continuous isoflurane-nitrous oxide anaesthesia there was no clinically significant lightening of anaesthesia and others have commented that during extensive use of tramadol intra-operatively over several years, there had not been any incidence of recall in any patient treated at their clinic.[3]

1. Lehmann KA, *et al.* Zur Bedeutung von Tramadol als intraoperativem Analgetikum: eine randomisierte Doppelblindstudie im Vergleich zu Placebo. *Der Anaesthetist* 1985; **34:** 11–19.
2. Coetzee JF, *et al.* Effect of tramadol on depth of anaesthesia. *Br J Anaesth* 1996; **76:** 415–18.
3. Budd K. Tramadol. *Br J Anaesth* 1995; **75:** 500.

Interactions

For interactions associated with opioid analgesics, see p.103.

Carbamazepine is reported to diminish the analgesic activity of tramadol by reducing serum concentrations.

The risk of seizures is increased if tramadol is used with other drugs that have the potential to lower the seizure threshold. See also Effects on the CNS under Adverse Effects, above.

Tramadol inhibits reuptake of noradrenaline and serotonin and enhances serotonin release and there is the possibility that it may interact with other drugs that enhance monoaminergic neurotransmission including lithium, tricyclic antidepressants, and SSRIs; it should not be given to patients receiving MAOIs or within 14 days of their discontinuation.

◊ Metabolism of tramadol is mediated by the cytochrome P450 isoenzyme CYP2D6. Use with specific inhibitors of this enzyme, such as *quinidine*, may increase concentrations of tramadol and lower concentrations of its active metabolite but the clinical consequences of this effect are unclear.

Anticoagulants. For reports of the effect of tramadol on oral anticoagulants, see Analgesics under Interactions of Warfarin, p.1427.

Antidepressants. For reference to possible cases of serotonin syndrome associated with use of tramadol and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p.397.

5-HT$_3$-receptor antagonists. The pre-operative use of *ondansetron* has been noted to reduce the postoperative analgesic efficacy of tramadol.[1,2] In one study,[1] the cumulative dose of tramadol was up to 35% greater in those patients who also received ondansetron compared to those who received no antiemetic. In addition there was no difference in the incidence of postoperative nausea and vomiting between the two groups.

1. De Witte JL, *et al.* The analgesic efficacy of tramadol is impaired by concurrent administration of ondansetron. *Anesth Analg* 2001; **92:** 1319–21.
2. Arcioni R, *et al.* Ondansetron inhibits the analgesic effects of tramadol: a possible 5-HT spinal receptor involvement in acute pain in humans. *Anesth Analg* 2002; **94:** 1553–7.

Pharmacokinetics

Tramadol is readily absorbed after oral doses but is subject to some first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use and 100% after intramuscular injection. Plasma protein binding is about 20%. Tramadol is metabolised by *N*- and *O*-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite *O*-desmethyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine, predominantly as metabolites. Tramadol is widely distributed, crosses the placenta, and appears in small amounts in breast milk. The elimination half-life is about 6 hours.

Children. References.

1. Murthy BVS, *et al.* Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. *Br J Anaesth* 2000; **84:** 346–9.
2. Payne KA, *et al.* Pharmacokinetics of oral tramadol drops for postoperative pain relief in children aged 4 to 7 years—a pilot study. *Anesth Prog* 2003; **49:** 109–12.
3. Zwaveling J, *et al.* Pharmacokinetics of rectal tramadol in postoperative paediatric patients. *Br J Anaesth* 2004; **93:** 224–7.
4. Garrido MJ, *et al.* Population pharmacokinetic/pharmacodynamic modelling of the analgesic effects of tramadol in pediatrics. *Pharm Res* 2006; **23:** 2014–23.
5. Saudan S, Habre W. Particularités pharmacologiques du tramadol chez l'enfant. *Ann Fr Anesth Reanim* 2007; **26:** 560–3.

The elderly. Pharmacokinetic parameters in elderly patients were found to be similar to those in younger patients.[1]

1. Likar R, *et al.* Pharmacokinetic and pharmacodynamic properties of tramadol IR and SR in elderly patients: a prospective, age-group—controlled study. *Clin Ther* 2006; **28:** 2022–39.

Metabolism. Production of the active metabolite *O*-desmethyltramadol is dependent on the cytochrome P450 isoenzyme CYP2D6, which exhibits genetic polymorphism.[1,2] For a reference to a debilitating CNS-mediated reaction in a patient who was an extensive metaboliser with high CYP2D6 activity, see Effects on the CNS under Adverse Effects, above.

1. Poulsen L, *et al.* The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; **60:** 636–44.
2. Pedersen RS, *et al.* Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol* 2006; **62:** 513–21.

Uses and Administration

Tramadol hydrochloride is an opioid analgesic (p.104). It also has noradrenergic and serotonergic properties

that may contribute to its analgesic activity. Tramadol is used for moderate to severe pain.

Tramadol hydrochloride is given by mouth, intravenously, or rectally as a suppository. The intramuscular route has also been used. It may also be given by infusion or as part of a patient-controlled analgesia system.

Usual oral doses are 50 to 100 mg every 4 to 6 hours. Tramadol hydrochloride may also be given orally as a modified-release preparation once or twice daily. The total oral daily dosage should not exceed 400 mg. Preparations containing tramadol hydrochloride with other analgesics such as paracetamol are also used.

A dose of 50 to 100 mg may be given every 4 to 6 hours by intramuscular or intravenous injection over 2 to 3 minutes, or by intravenous infusion. For the treatment of postoperative pain, the initial dose is 100 mg followed by 50 mg every 10 to 20 minutes if necessary to a total maximum (including the initial dose) of 250 mg in the first hour. Thereafter, doses are 50 to 100 mg every 4 to 6 hours up to a total daily dose of 600 mg.

Usual rectal doses by suppository are 100 mg up to 4 times daily.

For details of doses in children and in patients with hepatic or renal impairment, see below.

◊ References.

1. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. *Drugs* 2000; **60:** 139–76.
2. McClellan K, Scott LJ. Tramadol/paracetamol. *Drugs* 2003; **63:** 1079–86. Correction. *ibid.*; 1636.
3. Bennett RM, *et al.* Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med* 2003; **114:** 537–45.
4. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004; **43:** 879–923.
5. Leppert W, Luczak J. The role of tramadol in cancer pain treatment—a review. *Support Care Cancer* 2005; **13:** 5–17.
6. Close BR. Tramadol: does it have a role in emergency medicine? *Emerg Med Australas* 2005; **17:** 73–83.
7. Cepeda MS, *et al.* Tramadol for osteoarthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
8. Hollingshead J, *et al.* Tramadol for neuropathic pain. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/06/08).
9. Keating GM. Tramadol sustained-release capsules. *Drugs* 2006; **66:** 223–30.
10. Hair PI, *et al.* Tramadol extended-release tablets. *Drugs* 2006; **66:** 2017–27.
11. Lee EY, *et al.* Tramadol 37.5-mg/acetaminophen 325-mg combination tablets added to regular therapy for rheumatoid arthritis pain: a 1-week, randomized, double-blind, placebo-controlled trial. *Clin Ther* 2006; **28:** 2052–60.
12. Freeman R, *et al.* Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Curr Med Res Opin* 2007; **23:** 147–61.

Administration in children. In the UK, tramadol hydrochloride is licensed for the management of moderate to severe pain in children 12 years of age and older; usual adult doses may be given (see above). However, in some other European countries it is licensed in younger children although the age range permitted can vary: for example, in *France*, a usual dose in those aged 3 years and over is 1 to 2 mg/kg orally, which may be repeated 3 or 4 times daily, whereas in *Germany*, similar doses are permitted in children as young as 1 year old. Tramadol has also been given parenterally to children in doses similar to those used orally.

Some references on the use of tramadol in children.

1. Finkel JC, *et al.* An evaluation of the efficacy and tolerability of oral tramadol hydrochloride tablets for the treatment of postsurgical pain in children. *Anesth Analg* 2002; **94:** 1469–73.
2. Demiraran Y, *et al.* A comparison of the postoperative analgesic efficacy of single-dose epidural tramadol versus morphine in children. *Br J Anaesth* 2005; **95:** 510–13.
3. Bozkurt P. Use of tramadol in children. *Paediatr Anaesth* 2005; **15:** 1041–7.
4. Chu Y-C, *et al.* Intraoperative administration of tramadol for postoperative nurse-controlled analgesia resulted in earlier awakening and less sedation than morphine in children after cardiac surgery. *Anesth Analg* 2006; **102:** 1668–73.

Administration in hepatic or renal impairment. A dosage interval of 12 hours is recommended for tramadol usage in severe hepatic impairment. The dosage interval should also be increased to 12 hours in patients with a creatinine clearance (CC) less than 30 mL/minute; in the USA licensed product information suggests that the maximum oral dose should not exceed 200 mg daily in these patients. Tramadol should not be given to patients with more severe renal impairment (CC less than 10 mL/minute).

Preparations

BP 2008: Tramadol Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Adamon†; Calmador; Nobligan; Trama-Klosidol; Tramal; Tramalan†; ***Austral.:*** Tramahexal; Tramal; Tramedo; Zydol; ***Austria:*** Adamon; Contramal; Cromatodol; Dolol; Lanalget; Nycodol; Tradolan; Tramabene; Tramadolor; Tramal; Tramamed; Tramastad; Tramundal; Tramundin; ***Belg.:*** Contramal; Doctramado; Dolzam; Tradonal; Tramium; ***Braz.:*** Anangor; Dorless; Sensitram; Sylador; Timasen†; Trabilin; Tramadon; Tramal; Tramaliv; Zamadol; ***Chile:*** Manol; Minidol; Timarol; Tramal; Zodol; ***Cz.:*** Mabron; Noax Uno; Protradon; Trabar†; Tradef; Tradonal†; Tralgit; Tramabene; Tramagit; Tramal; Tramundin; ***Denm.:*** Dolol; Mandolgin; Nobligan; Tadol; Tradolan; ***Fin.:*** Tradolan; Tramadin; Tramagetic; Tramal; Trambo; ***Fr.:*** Biodalgic; Contramal; Monocrixo; Orozamudol; Takadol; Topalgic; Trasedal†; Zamudol; Zumalgic; ***Ger.:*** Amadol; Jutadol; T-long; Tial; Tradol†; Trama; Trama-Dorsch†; Tramabeta; Tramadoc; Tramadolor; Tramadura; Tramagetic†; Tramagit; Tramal; Tramundin; Travex One; ***Gr.:*** Tramal; ***Hong Kong:*** Acugesic; Mabron; Sefmal; Tradonal†; Tramal; Tramo; ***Hung.:*** Adamon; Contramal; Ralgen; Tramadolor; Tramalgic; ***India:*** Contramal; Tramacip; Tramazac; TRD-Contin; Urgendol; ***Indon.:*** Andalpha; Bellatram; Camigesik; Contram; Dolana; Dolgesik; Dolocap; Forgesic; Kamadol; Katrasic; Nonalges; Nufapotram; Orasic; Pinorec; Radol; Simatral; Tradosik; Tradyl; Tragesik; Tramal; Trasik; Traumasik; Trunal; Tugesal; Zumatram; ***Irl.:*** Biodol; By-Madol; Tradol; Tramake; Tramapine; Tramex; Xymel; Zamadol; Zydol; ***Israel:*** Trabar; Tramadex; Tramal; ***Ital.:*** Adamon; Contramal; Fortradol; Fraxidol; Prontalgin; Tradonal; Traflash; Tralodie; Tramalin; ***Malaysia:*** Acugesic; Analab; Mabron; Pengesic; Sefmal; Tracidol; Tramada; Tramal†; Tramundin; ***Mex.:*** Durodor; Nobligan; Prontofort; Tradol; Tralic; Tramed; Trexol; Veldrol; ***Neth.:*** Doltard; Theradol; Tradonal; Tramagetic; Tramal; Tramelene; ***Norw.:*** Nobligan; Tradolan; Tramagetic; ***NZ:*** Tramal; Tramedo; Zytram; ***Philipp.:*** Dolmal; Dolotral; Dolpaz; Milador; Pengesic; Peptrad; Siverol; TDL; Tolma; Tradonal; Tramal; Tramkor; Tramundin; Unitral; ***Pol.:*** Poltram; Tramahexal; Tramal; Tramcod; Tramundin; ***Port.:*** Dolpar; Gelotralib; Nobligan; Paxilfar; Tramal; Tramy; Travex; Zydol; Zytram; ***Rus.:*** Mabron (Маброн); Sintradon (Синтрадон); Tramal (Трамал); ***S.Afr.:*** Dolotram; Tramahexal; Tramal; Tramazac; ***Singapore:*** Mabron; Pengesic; Sefmal; Tradol†; Tramal; Tramium; ***Spain:*** Adolonta; Ceparidin; Dolodol; Sofrodol; Tioner; Tradonal; Tralgiol; Zytram; ***Swed.:*** Nobligan; Tiparol; Tradolan; ***Switz.:*** Dolotramine; Ecodolor; Tramal; Tramkor; Tramundin; ***Thai.:*** Amanda; Ammitram; Anadol; Analab; Mabron†; Madol; Madola; Millidol; Paindol†; Pharmadol; Rofy; Sefmal; Tamolan; Tracine; Tradolgesic; Tradonal; Tramadil; Tramal; Tramamed; Tramax; Tramoda; Trosic; Volcidol-S; ***Turk.:*** Contramal; Tramadolor; ***UK:*** Dromadol; Larapam; Mabron; Nobligan; Tradorec; Tramake; Tramulief; Zamadol; Zeridame; Zydol; ***USA:*** Ultram; ***Venez.:*** Tramal.

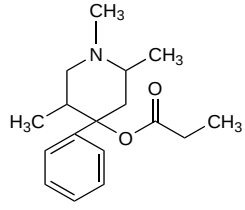
Multi-ingredient: ***Arg.:*** Calmador Plus; Tramacet; ***Austria:*** Zaldiar; ***Belg.:*** Zaldiar; ***Braz.:*** Ultracet; ***Canad.:*** Tramacet; ***Chile:*** Cronus; Minidol Plus; Zafin; Zaldiar; ***Cz.:*** Zaldiar; ***Fr.:*** Ixprim; Zaldiar; ***Ger.:*** Zaldiar; ***Hong Kong:*** Ultracet; ***India:*** Tolydol; Tramacip Plus; Ultrazac; ***Malaysia:*** Ultracet; ***Mex.:*** Gammadol; Sinergix; Tramacet; Zaldiar; ***Neth.:*** Tilalgin; Zaldiar; ***Philipp.:*** Dolcet; ***Pol.:*** Zaldiar; ***Port.:*** Tilalgin; Zaldiar; ***Rus.:*** Zaldiar (Залдиар); ***S.Afr.:*** Tramacet; ***Singapore:*** Ultracet; ***Spain:*** Pazital; Pontalsic; Zaldiar; ***Switz.:*** Zaldiar; ***Thai.:*** Ultracet; ***UK:*** Tramacet; ***USA:*** Ultracet; ***Venez.:*** Ultracet; Zaldiar.

Trimeperidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimeperidina; Promedol (trimeperidine); Promedolum (trimeperidine); Trimépéridine, Chlorhydrate de; Trimeperidini Hydrochloridum. 1,2,5-Trimethyl-4-phenyl-4-piperidyl propionate hydrochloride.

Тримеперидина Гидрохлорид

$C_{17}H_{25}NO_2$,HCl = 311.8.
CAS — 64-39-1 (trimeperidine); 125-80-4 (trimeperidine hydrochloride).



(trimeperidine)

Profile

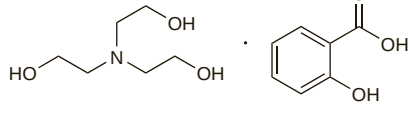
Trimeperidine hydrochloride is an opioid analgesic (p.101) with actions and uses similar to those of pethidine (p.113).

Trolamine Salicylate *(pINNM)*

Salicilato de trietanolamina; Triethanolamine Salicylate; Trolamine, Salicylate de; Trolamini Salicylas.

Троламина Салицилат

$C_{13}H_{21}NO_6$ = 287.3.
CAS — 2174-16-5.



Pharmacopoeias. In *US*.
USP 31 (Trolamine Salicylate). A compounded mixture of trolamine and salicylic acid in propylene glycol. pH of a 5% solution in water is between 6.5 and 7.5. Store in airtight containers in a cool place.

Profile

Trolamine salicylate is a salicylic acid derivative used similarly to methyl salicylate (p.85) in topical rubefacient preparations in a concentration of 10 to 20% for the relief of muscular and rheumatic pain. It has also been used as a sunscreen.

Percutaneous absorption. In contrast to methyl salicylate, which undergoes considerable absorption and produces high subcutaneous and dermal concentrations of salicylic acid after application to intact skin, concentrations of salicylic acid after topical application of trolamine salicylate were substantially lower in tissue[1] and undetectable in serum.[2]

1. Cross SE, *et al.* Is there tissue penetration after application of topical salicylate formulations? *Lancet* 1997; **350:** 636.
2. Morra P, *et al.* Serum concentrations of salicylic acid following topically applied salicylate derivatives. *Ann Pharmacother* 1996; **30:** 935–40.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Geniol Flex†; ***Austral.:*** Dencorub Arthritis; Goanna Arthritis Cream; Metsal AR Analgesic; ***Canad.:*** Antiphlogistine Rub A-535 No Odour; Aspercreme; Bengay No Odor; Myoflex; ***Mex.:*** Myoflex; ***Singapore:*** Metsal AR Analgesic; ***Spain:*** Bexidermil; ***USA:*** Analgesia Creme; Aspercreme; Coppertone Tan Magnifier; Flex-Power Performance Sports; Mobisyl; Myoflex; Sportscreme; Tropical Blend Tan Magnifier.

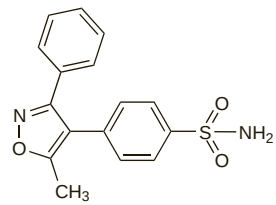
Multi-ingredient: ***Arg.:*** Duo Minoxi†; ***Canad.:*** Myoflex Extra Strength Ice.

Valdecoxib *(BAN, USAN, rINN)*

SC-65872; Valdécoxib; Valdecoxibum; Valdekoksib. *p*-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide.

Вальдекоксиб

$C_{16}H_{14}N_2O_3S$ = 314.4.
CAS — 181695-72-7.
ATC — M01AH03.
ATC Vet — QM01AH03.



Profile

Valdecoxib is an NSAID (p.96) reported to be a selective inhibitor of cyclo-oxygenase-2 (COX-2). It was given orally in the treatment of osteoarthritis and rheumatoid arthritis, and for the pain of dysmenorrhoea. The risk of serious skin reactions with valdecoxib, in addition to its cardiovascular adverse effects (see below), prompted its general withdrawal worldwide in April 2005.

Effects on the cardiovascular system. The short-term use of parecoxib and valdecoxib after coronary artery bypass graft surgery has been associated with an increased risk of adverse effects such as myocardial infarction, deep-vein thrombosis, pulmonary embolism, and stroke.[1] When compared with patients in the placebo group, the risk of such effects was almost 4 times greater in those who had received intravenous parecoxib for 3 days followed by oral valdecoxib for the next 7 days. Those patients who received oral valdecoxib only for 7 days postoperatively had a non-significant increase in risk for adverse cardiovascular effects.

The adverse cardiovascular effects associated with valdecoxib treatment were one of the reasons the drug was generally withdrawn in April 2005.

1. Nussmeier NA, *et al.* Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005; **352:** 1081–91.

Effects on the skin. Toxic epidermal necrolysis developed in a patient who took valdecoxib for 8 days, despite stopping the drug at the first signs of a rash and starting treatment with oral prednisolone;[1] the patient had a history of hypersensitivity to sulfonamides. Health Canada[2] noted in January 2004 that it had received 5 reports of serious cutaneous adverse reactions associated with valdecoxib over less than 1 year from marketing of the drug in December 2002. However, none of these were erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis although such reactions had been reported to other regulatory authorities. In December 2004, the EMEA[3] stated that it had received reports of all 3 reactions, as well as exfoliative dermatitis; most of them had occurred within the first 2 weeks of starting treatment and the incidence rate appeared greater for valdecoxib than other selective COX-2 inhibitors. The EMEA also noted that use of parecoxib (a prodrug of valdecoxib, see p.111) had been associated with erythema multiforme.

The increased risk of serious skin reactions with valdecoxib treatment was one of the reasons the drug was generally withdrawn in April 2005.

1. Glasser DL, Burroughs SH. Valdecoxib-induced toxic epidermal necrolysis in a patient allergic to sulfa drugs. *Pharmacotherapy* 2003; **23:** 551–3.