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.

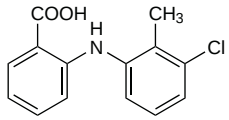
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Tinalox; Valoron†; Valtran; ***Cz.:*** Valoron†; ***Ger.:*** Andolor; Celldolor; Findol N†; Gruntin Tropfen†; Nalidin; Tili Comp; Tili-Puren; Tili†; Tilicomp; Tilidalor†; Tilidin comp; Tilidin N; Tilidin plus; Tilidin-saar; Tilidura;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

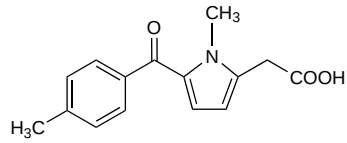
Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Flocur; ***Austria:*** Migea; ***Braz.:*** Fenamic†; ***Cz.:*** Migea; ***Denm.:*** Clotam†; Migea; ***Fin.:*** Clotam; Migea†; ***Gr.:*** Clotam; Gantil; Polmonin; Primactam; Purfalox; Tolfamic; Turbaund; ***Mex.:*** Bifenac†; 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.

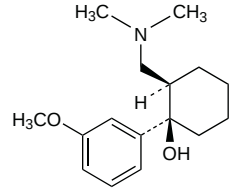
Tramadol Hydrochloride

(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.