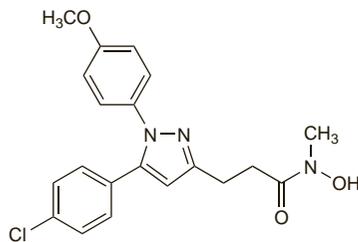


Teopoxalin (USAN, rINN)

ORF-20485; RWJ-20485; Tepoksaliini; Tepoxalina; Тэпоксалин; Tepoxalinum. 5-(p-Chlorophenyl)-1-(p-methoxyphenyl)-N-methylpyrazole-3-propionhydroxamic acid.

Тепоксалин
C₂₀H₂₀ClN₃O₃ = 385.8.
CAS — 103475-41-8.
ATC Vet — QM01AE92.

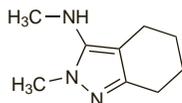
**Profile**

Teopoxalin, a propionic acid derivative, is an NSAID used in veterinary medicine for the treatment of inflammation and pain in dogs.

Tetridamine (rINN)

POLI-67; Tetridamina; Тэтридамин; Tetridaminum; Tetrydamine (USAN). 4,5,6,7-Tetrahydro-2-methyl-3-(methylamino)-2H-indazole.

Тетридамин
C₉H₁₅N₃ = 165.2.
CAS — 17289-49-5.

**Profile**

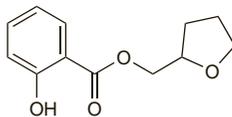
Tetridamine is an NSAID (p.96) that has been used as the maleate as a douche in the treatment of vaginitis.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Deb; **Spain:** Fomene.

Thurfyl Salicylate

Salicilato de turfilo. Tetrahydrofurfuryl salicylate.
C₁₂H₁₄O₄ = 222.2.
CAS — 2217-35-8.

**Profile**

Thurfyl salicylate is a salicylic acid derivative that has been used similarly to methyl salicylate (p.85) in topical rubefacient preparations at concentrations of up to 14% for musculoskeletal, joint, peri-articular, and soft-tissue disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

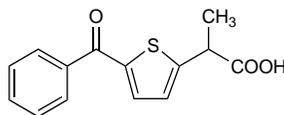
Multi-ingredient: **Austral.:** Biosal Arthritis; **Belg.:** Transvane; **Ir.:** Transvasin; **UK:** Transvasin Heat Rub.

Tiaprofenic Acid (BAN, rINN)

Acide tiaprofénique; Ácido tiaprofénico; Acidum tiaprofenicum; FC-3001; Kyselina tiaprofenová; RU-15060; Tiaprofeeniappo; Tiaprofenik Asit; Tiaprofeno rūgštis; Tiaprofensyra. 2-(5-Benzoyl-2-thienyl)propionic acid.

Тиaproфеновая Кислота
C₁₄H₁₂O₃S = 260.3.
CAS — 33005-95-7.
ATC — M01AE11.
ATC Vet — QM01AE11.

The symbol † denotes a preparation no longer actively marketed

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

Ph. Eur. 6.2 (Tiaprofenic Acid). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol, in acetone, and in dichloromethane. Protect from light.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Tiaprofenic acid may cause cystitis, bladder irritation, and other urinary-tract symptoms (see below). It should not be given to patients with active urinary-tract disorders or prostatic disease or a history of recurrent urinary-tract disorders. It should be stopped immediately if urinary-tract symptoms occur and urinalysis and urine culture performed.

Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment.

Breast feeding. Although tiaprofenic acid is distributed into breast milk, the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. Licensed product information also states that exposure to tiaprofenic acid via breast milk is unlikely to be of pharmacological significance; however, it is recommended that either treatment or breast feeding is stopped as necessary.

Effects on the urinary tract. Cystitis and bladder irritation have been associated with the use of tiaprofenic acid.¹⁻⁶ In August 1994 the UK CSM stated⁴ that since the introduction of tiaprofenic acid in the UK in 1982 they had received 69 reports of cystitis and 32 other reports of urinary-tract symptoms associated with tiaprofenic acid including frequency, dysuria, and haematuria whereas only 8 cases of cystitis had been reported for all other NSAIDs combined. Analysis of spontaneous reports received by WHO⁷ confirmed that cystitis was more commonly associated with tiaprofenic acid than with other NSAIDs. The Australian Adverse Drug Reactions Advisory Committee had received similar reports.³ Since the 1994 warning, the CSM⁸ had received reports of a further 74 cases of cystitis, but the majority of these had occurred before the warning was issued. The duration of treatment in patients affected had varied considerably. Most patients recovered when tiaprofenic acid was withdrawn.

The CSM recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and that it should be stopped in patients who develop urinary-tract symptoms. Patients should be advised that if they develop symptoms such as urinary frequency, nocturia, urgency, or pain on urination, or have blood in their urine they should stop taking tiaprofenic acid and consult their doctor. Older patients may be at increased risk.⁹

- Ahmed M, Davison OW. Severe cystitis associated with tiaprofenic acid. *BMJ* 1991; **303**: 1376.
- O'Neill GFA. Tiaprofenic acid as a cause of non-bacterial cystitis. *Med J Aust* 1994; **160**: 123-5.
- Australian Adverse Drug Reactions Advisory Committee (ADRAC). Update on tiaprofenic acid and urinary symptoms. *Aust Adverse Drug React Bull* 1994; **13**: 6.
- CSM/MCA. Severe cystitis with tiaprofenic acid (Surgam). *Current Problems* 1994; **20**: 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&DocName=CON2015615&RevisionSelectionMethod=LatestReleased (accessed 08/11/07)
- Harrison WJ, et al. Adverse reactions to tiaprofenic acid mimicking interstitial cystitis. *BMJ* 1994; **309**: 574.
- Mayall FG, et al. Cystitis and ureteric obstruction in patients taking tiaprofenic acid. *BMJ* 1994; **309**: 599.
- The ADR Signals Analysis Project (ASAP) Team. How does cystitis affect a comparative risk profile of tiaprofenic acid with other non-steroidal antiinflammatory drugs? An international study based on spontaneous reports and drug usage data. *Pharmacol Toxicol* 1997; **80**: 211-17.
- Crawford MLA, et al. Severe cystitis associated with tiaprofenic acid. *Br J Urol* 1997; **79**: 578-84.
- Buchbinder R, et al. Clinical features of tiaprofenic acid (surgam) associated cystitis and a study of risk factors for its development. *J Clin Epidemiol* 2000; **53**: 1013-19.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Tiaprofenic acid is absorbed from the gastrointestinal tract with peak plasma concentrations being reached within about 1.5 hours after oral doses. It has a short elimination half-life of about 2 hours and is highly bound to plasma proteins (about 98%). Excretion of tiaprofenic acid and its metabolites is mainly in the urine in the form of acyl glucuronides; some is excreted in the bile. Tiaprofenic acid crosses the placenta and is distributed into breast milk.

References

- Davies NM. Clinical pharmacokinetics of tiaprofenic acid and its enantiomers. *Clin Pharmacokinet* 1996; **31**: 331-47.

Uses and Administration

Tiaprofenic acid, a propionic acid derivative, is an NSAID (p.99). It is used for the relief of pain and inflammation in musculoskeletal and joint disorders such as ankylosing spondylitis,

osteoarthritis, and rheumatoid arthritis, in peri-articular disorders such as fibrositis and capsulitis, and in soft-tissue disorders such as sprains and strains. The usual oral dose is 600 mg daily given in 2 or 3 divided doses; in patients with cardiac, hepatic, or renal impairment, licensed product information suggests that the dose is reduced to 200 mg twice daily. A modified-release preparation may be available for once-daily use. Tiaprofenic acid has also been given rectally. It has been given intramuscularly as the trometamol salt in acute conditions.

References

- Plosker GL, Wagstaff AJ. Tiaprofenic acid: a reappraisal of its pharmacological properties and use in the management of rheumatic diseases. *Drugs* 1995; **50**: 1050-75.

Administration in hepatic or renal impairment. Tiaprofenic acid is contra-indicated in patients with severe hepatic or renal impairment; for dosage details in those with more moderate impairment, see Uses and Administration, above.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Surgam; **Canad.:** Albert Tiafen†; Surgam; **Cz.:** Surgam; Thialgin; **Denm.:** Surgam†; **Fin.:** Surgam†; **Fr.:** Flanid; Surgam; **Ger.:** Surgam; **Hung.:** Surgam; **Ir.:** Surgam; **Ital.:** Suralgan†; Surgam†; Tiaprofen†; **Mex.:** Surgam; **Neth.:** Surgam; **NZ:** Surgam; **Pol.:** Surgam; **Port.:** Surgam; **S.Afr.:** Surgam; **Thal.:** Fengam; Surgam†; **Turk.:** Surgam; **UK:** Surgam; **Venez.:** Torpas.

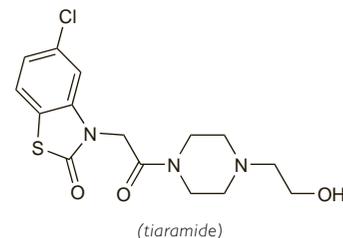
Tiamide Hydrochloride (BANM, USAN, rINNM)

Hydrocloruro de tiamida; NTA-194; Tiaperamide Hydrochloride; Tiamide, Chlorhydrate de; Tiamidi Hydrochloridum. 5-Chloro-3-[2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl]benzothiazolin-2-one hydrochloride.

Тиарамид Гидрохлорид

C₁₅H₁₈ClN₃O₂S.HCl = 392.3.

CAS — 32527-55-2 (tiamide); 35941-71-0 (tiamide hydrochloride).

**Pharmacopoeias.** In *Jpn.***Profile**

Tiamide hydrochloride is an NSAID (p.96) that has been given orally for the relief of pain and inflammation.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Solantal†.

Tilidine Hydrochloride (USAN, pINNM)

Gö 1261-C; Hydrocloruro de tilidina; Tilidate Hydrochloride (BANM); Tilidiinihydroklonidihemihydraatti; Tilidine, Chlorhydrate de; Tilidine (chlorhydrate de) hemihydraté; Tilidinhydroklonid hemihydrát; Tilidinhydroklonid hemihydrát; Tilidini Hydrochloridum; Tilidini hydrochloridum hemihydratum; Tilidino hydrochloridas hemihidratas; W-5759A. (±)-Ethyl trans-2-dimethylamino-1-phenylcyclohex-3-ene-1-carboxylate hydrochloride hemihydrate.

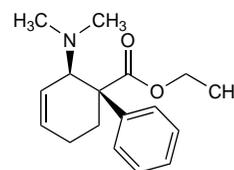
Тилидина Гидрохлорид

C₁₇H₂₃NO₂.HCl. / H₂O = 318.8.

CAS — 20380-58-9 (tilidine); 27107-79-5 (anhydrous tilidine hydrochloride); 24357-97-9 (anhydrous +-trans-tilidine hydrochloride).

ATC — N02AX01.

ATC Vet — QN02AX01.



(tilidine)

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

Ph. Eur. 6.2 (Tilidine Hydrochloride Hemihydrate). A white or almost white, crystalline powder. A suitable antioxidant may be

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 (bisonortilidate). 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; Tildalor; Tildin comp; Tildin N; Tildin plus; Tildin-saar; Tildura; Tilgetic; TiliMerck; Tinalox; Valoron N; **S.Afr.:** Valoron; **Switz.:** Valoron.

Tolfenamic Acid (BAN, INN)

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

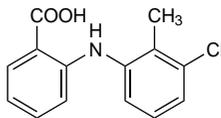
Толфенамовая Кислота

$C_{14}H_{12}ClNO_3 = 261.7$.

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; **Gantli:** Polmonin; **Primaclam;** **Purifalox;** **Tolfamic;** **Turbaund;** **Mex.:** Bifenac; **Flocur;** **Neth.:** Clotam; **Rocidylm;** **Norw.:** Migea; **Pol.:** Migea; **Swed.:** Migea; **Switz.:** Clotam; **UK:** Clotam; **Venez.:** Clotam.

Tolmetin Sodium (BANM, USAN, rINNM)

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

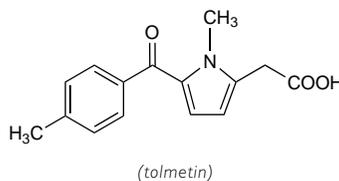
Натрий Тольметин

$C_{15}H_{14}NNaO_3 \cdot 2H_2O = 315.3$.

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 considers¹ 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 agranulocytosis¹ and thrombocytopenia² 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 reported¹ 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 nephritis¹ 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 meningitis³ 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; Tramadolhydrochlorid; Tramadolhydrochloridum; Tramadolhydrochlorid; Tramadolhydrochlorid; Tramadolhydrochlorid; U-26225A. (±)-trans-2-Dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexanol hydrochloride.

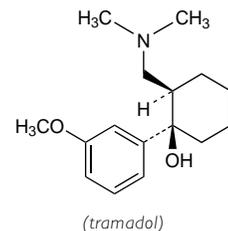
Трамাদола Гидрохлорид

$C_{16}H_{25}NO_2 \cdot HCl = 299.8$.

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 study¹ 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.