4. Colivicchi F, *et al.* Ticlopidine-induced chronic cholestatic hepatitis: a case report. *Curr Ther Res* 1994; **55:** 929–31.
5. Mambelli E, *et al.* Severe ticlopidine-induced cholestatic syndrome. *Blood Purif* 2007; **25:** 441–5.
6. Ruiz-Valverde P, *et al.* Ticlopidine-induced granulomatous hepatitis. *Ann Pharmacother* 1995; **29:** 633–4.
7. Zeolla MM, Carson JJ. Successful use of clopidogrel for cerebrovascular accident in a patient with suspected ticlopidine-induced hepatotoxicity. *Ann Pharmacother* 1999; **33:** 939–41.
8. Willens HJ. Clopidogrel-induced mixed hepatocellular and cholestatic liver injury. *Am J Ther* 2000; **7:** 317–18.

Effects on the lungs. Bronchiolitis obliterans-organising pneumonia developed in a 76-year-old woman receiving ticlopidine and prednisone for temporal arteritis.[1] The condition resolved over several months when ticlopidine was withdrawn.

1. Alonso-Martinez JL, *et al.* Bronchiolitis obliterans-organizing pneumonia caused by ticlopidine. *Ann Intern Med* 1998; **129:** 71–2.

Interactions

Ticlopidine should be used with caution in patients receiving other drugs, such as anticoagulants and antiplatelets, that increase the risk of bleeding. Ticlopidine is an inhibitor of cytochrome P450, including the isoenzymes CYP2C19, CYP2D6, and CYP2B6, and may inhibit the metabolism of other drugs that are metabolised by this route. The clearance of ticlopidine may be reduced by cimetidine. Corticosteroids may antagonise the effect of ticlopidine on bleeding time.

Anticoagulants. Use of ticlopidine with anticoagulants may increase the risk of bleeding. However, ticlopidine has been reported to antagonise the effect of *acenocoumarol* (see Antiplatelets under Interactions of Warfarin, p.1429).

Antiepileptics. For a report of acute *phenytoin* toxicity in a well-stabilised patient following addition of ticlopidine, see p.500.

Xanthines. For reference to the effect of ticlopidine on *theophylline* half-life, see p.1145.

Pharmacokinetics

Ticlopidine is rapidly and almost completely absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins. The terminal half-life during chronic dosing is reported to be about 30 to 50 hours. Ticlopidine is extensively metabolised in the liver. About 60% of a dose is excreted in the urine as metabolites and 25% in the faeces.

◊ References.

1. Desager J-P. Clinical pharmacokinetics of ticlopidine. *Clin Pharmacokinet* 1994; **26:** 347–55.
2. Buur T, *et al.* Pharmacokinetics and effect of ticlopidine on platelet aggregation in subjects with normal and impaired renal function. *J Clin Pharmacol* 1997; **37:** 108–15.

Uses and Administration

Ticlopidine hydrochloride is a thienopyridine antiplatelet drug used in thromboembolic disorders (p.1187). It appears to act by inhibiting adenosine diphosphate-mediated platelet aggregation. It may be given prophylactically as an alternative to aspirin in patients at risk of thrombotic stroke (p.1185) and in the management of intermittent claudication (see Peripheral Vascular Disease, p.1178) and ischaemic heart disease. It is also licensed as an adjunct to aspirin for the prevention of subacute stent occlusion after intracoronary stenting (but see Reperfusion and Revascularisation Procedures, below). Ticlopidine may also be used to prevent occlusion and platelet loss during extracorporeal circulatory procedures.

In the prevention of thrombotic **stroke**, and in **intermittent claudication**, ticlopidine hydrochloride is given orally in a dose of 250 mg twice daily, with meals. For the prevention of subacute stent occlusion after **intracoronary stenting** ticlopidine hydrochloride is given in a dose of 250 mg twice daily for 4 weeks, starting at the time of stent placement.

Regular haematological monitoring is required during ticlopidine therapy (see Adverse Effects and Precautions, above).

◊ References.

1. McTavish D, *et al.* Ticlopidine: an updated review of its pharmacology and therapeutic use in platelet-dependent disorders. *Drugs* 1990; **40:** 238–59.
2. Flores-Runk P, Raasch RH. Ticlopidine and antiplatelet therapy. *Ann Pharmacother* 1993; **27:** 1090–8.
3. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129:** 394–405.

Reperfusion and revascularisation procedures. Coronary stents are widely used as an adjunct to angioplasty to prevent acute vessel closure and to reduce restenosis (see Reperfusion and Revascularisation Procedures, p.1181). Subacute thrombosis is a major complication of their use and patients were initially treated with an aggressive combination of anticoagulants and antiplatelets. However, it is now generally recognised that antiplatelet drugs alone are adequate in most patients.

Early studies[1-4] found that ticlopidine for 4 to 6 weeks after stenting, given with long-term aspirin, was at least as effective as an oral anticoagulant with aspirin, with some studies showing benefit in terms of thrombosis[1,4] or bleeding complications.[1] However, the risk of neutropenia limits the use of ticlopidine, and clopidogrel is now generally preferred, although there is some evidence[5] that shorter courses of ticlopidine (2 weeks) may be acceptable.

Ticlopidine has also been reported[6] to improve the long-term patency of saphenous vein bypass grafts used to treat peripheral vascular disease in the legs.

1. Schömig A, *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; **334:** 1084–9.
2. Kastrati A, *et al.* Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial. *Circulation* 1997; **96:** 462–7.
3. Bertrand ME, *et al.* Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the Full Anticoagulation versus Aspirin and Ticlopidine (FANTASTIC) study. *Circulation* 1998; **98:** 1597–1603.
4. Leon MB, *et al.* A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998; **339:** 1665–71.
5. Berger PB, *et al.* Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. *Circulation* 1999; **99:** 248–53.
6. Becquemin J-P. Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. *N Engl J Med* 1997; **337:** 1726–31.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Dosier; Ticlid; Trombenal; ***Austral.:*** Ticlid; Tilodene; ***Austria:*** Thrombodine; Ticlodone; Tiklid; ***Belg.:*** Ticlid; ***Braz.:*** Plaketar; Ticlid; Ticlobal; ***Canad.:*** Ticlid; ***Chile:*** Ateroclar; Plaquetil; Ticlid; ***Cz.:*** Aplaket†; Apo-Tic; Ipaton; Platigren†; Tagren; Ticlid; ***Fr.:*** Ticlid; Ticlomed†; ***Ger.:*** Desiticlopidin; Tiklyd; ***Gr.:*** Anchostam-100†; Anghostam-100; Etfariol; Neo Fulvigal; Neoomnipen; Ruxicolan; Ticlid; Ticlodone; ***Hong Kong:*** Aplaket; Ticlid; Tipidin; ***Hung.:*** Aclotin; Aplatic; Ipaton; Placor; Ticlid; ***India:*** Ticlobest; Ticlop; Ticlopid; Tikleen†; Tyklid; ***Indon.:*** Agulan; Cartrilet; Goclid; Nufaclapide; Piclodin; Ticard; Ticlid; Ticlon; Ticuring; ***Israel:*** Ticlidil; ***Ital.:*** Anagregal†; Antigreg; Aplaket; Clox; Fluilast; Flupid; Fluxidin; Klodin; Opteron; Parsilid†; Ticlodone; Ticlogi†; Ticloproge†; Tiklid; ***Jpn:*** Panaldine; ***Malaysia:*** Antigreg; Aplaket; Ticlid; Ticlopine; Tipidin; ***Mex.:*** Ticlid; ***Norw.:*** Ticlid; ***Philipp.:*** Clotidone; Ticlid; ***Pol.:*** Aclotin; Apo-Clodin; Iclopid; Ifapidin; Ticlid; Ticlo; ***Port.:*** Agregamina†; Aplaket; Betlife; Isaxion†; Klodipin; Movin; Opidina†; Plaquetal; Previta; Ticlodix; Ticlopat; Tiklyd; Tiropa; Trombopat; ***Rus.:*** Ticlo (Тикло); Tikleen (Тиклин); ***S.Afr.:*** Ticlid†; ***Singapore:*** Antigreg; Aplaket; Tacron†; Ticlid; Tipidin; ***Spain:*** Ticlodone; Tiklid; ***Swed.:*** Ticlid; ***Thai.:*** Aplaket; Cenpidine; Siclot; Ticdine†; Ticlid; Ticlo; Ticlopine; Tikol†; Tilopin; Tipidine; Viladil; ***Turk.:*** Agretik; Ticlid; Ticlocard; ***UAE:*** Ticopar; ***USA:*** Ticlid; ***Venez.:*** Ticlid; Ticlopin†.

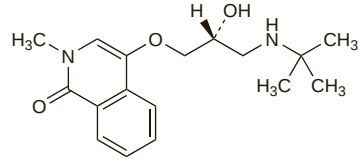
Tilisolol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de tilisolol; N-696; Tilisolol, Chlorhydrate de; Tilisololi Hydrochloridum. (±)-4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-2-methylisocarbostyril hydrochloride.

Тилизолола Гидрохлорид

$C_{17}H_{24}N_2O_3$,HCl = 340.8.

CAS — 85136-71-6 (tilisolol); 62774-96-3 (tilisolol hydrochloride).



Profile

Tilisolol hydrochloride is a non-cardioselective beta blocker (p.1225) with direct vasodilator activity. It is used in the management of angina pectoris (p.1157) and hypertension (p.1171) in oral doses of 10 to 20 mg once daily; up to a maximum of 30 mg once daily may be used if necessary.

Preparations

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

Timolol Maleate *(BANM, USAN, rINNM)* ⊗

Maleato de timolol; MK-950; Timolol Maleat; Timolol, maléate de; Timolol maleinát; Timololi maleas; Timololimaleaatti; Timololio maleatas; Timololmaleat; Timolol-maleát. (*S*)-1-*tert*-Butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol maleate.

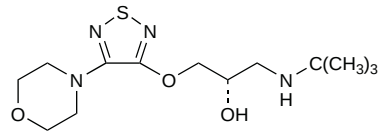
Тимолола Малеат

$C_{13}H_{24}N_4O_3S,C_4H_4O_4$ = 432.5.

CAS — 26839-75-8 (timolol); 91524-16-2 (timolol hemihydrate); 26921-17-5 (timolol maleate).

ATC — C07AA06; S01ED01.

ATC Vet — QC07AA06; QS01ED01.



(timolol)

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

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Timolol Maleate). A white or almost white, crystalline powder or colourless crystals. Soluble in water and in alcohol. A 2% solution in water has a pH of 3.8 to 4.3. Protect from light.
USP 31 (Timolol Maleate). A white to practically white, odourless or practically odourless powder. Soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform and in propylene glycol; insoluble in cyclohexane and in ether. A 2% solution in water has a pH of 3.8 to 4.3.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Timolol is distributed into breast milk. After instillation of timolol 0.5% eye drops twice daily, concentrations of timolol in breast milk of a woman were about 6 times greater than those in serum, the values being 5.6 and 0.93 nanograms/mL respectively.[1] In a study[2] in patients given oral timolol 5 mg three times daily, the mean concentration in breast milk was 15.9 nanograms/mL, and the ratio of milk to plasma concentrations was 0.8; a similar ratio was found at higher doses, and the authors considered that the amount ingested by an infant would not be important. No adverse effects were seen in these studies and the American Academy of Pediatrics considers[3] that timolol is therefore usually compatible with breast feeding.

1. Lustgarten JS, Podos SM. Topical timolol and the nursing mother. *Arch Ophthalmol* 1983; **101:** 1381–2.
2. Fidler J, *et al.* Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; **90:** 961–5.
3. 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 10/01/08)

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of timolol and that the dose of timolol may need to be reduced if used together.

Pharmacokinetics

Timolol is almost completely absorbed from the gastrointestinal tract but is subject to moderate first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose. Low concentrations are also found in plasma after use as eye drops. Timolol has low to moderate lipid solubility. Protein binding is reported to be low. Timolol crosses the placenta and is distributed into breast milk. A plasma half-life of 4 hours has been reported. Timolol is extensively metabolised in the liver, the metabolites being excreted in the urine with some unchanged timolol. Timolol is not removed by haemodialysis.

Metabolism. Timolol appears to be metabolised[1] by the cytochrome P450 isoenzyme CYP2D6 and studies[2-4] have shown that it is influenced by genetic polymorphism.

1. Volotinen M, *et al.* Timolol metabolism in human liver microsomes is mediated principally by CYP2D6. *Drug Metab Dispos* 2007; **35:** 1135–41.
2. McGourty JC, *et al.* Pharmacokinetics and beta-blocking effects of timolol in poor and extensive metabolizers of debrisoquin. *Clin Pharmacol Ther* 1985; **38:** 409–13.
3. Lewis RV, *et al.* Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1985; **19:** 329–33.
4. Lennard MS, *et al.* Timolol metabolism and debrisoquine oxidation polymorphism: a population study. *Br J Clin Pharmacol* 1989; **27:** 429–34.

Uses and Administration

Timolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Timolol is used as the maleate in the management of glaucoma (p.1873), hypertension (p.1171), angina pectoris (p.1157), and myocardial infarction (p.1175). It is also used in the prophylactic treatment of migraine (p.616). The hemihydrate is also used.

Eye drops containing timolol maleate or hemihydrate equivalent to 0.25 and 0.5% of timolol are instilled twice daily to reduce **raised intra-ocular pressure** in open-angle **glaucoma** and ocular hypertension. Once-daily use may suffice when the intra-ocular pressure has been controlled. Gel-forming eye drops are also available that are instilled once daily.

For other indications timolol is given orally. In **hypertension** timolol maleate is usually given in initial doses of 10 mg daily, increased according to response at intervals of 7 or more days. Usual maintenance doses are 10 to 40 mg daily, but doses up to 60 mg daily may be required in some patients; doses above 30 mg daily should be given in 2 equally divided doses.

In **angina pectoris** the initial dose is 5 mg twice daily, increased at intervals of 3 or more days by 10 mg daily. Most patients respond to 35 to 45 mg daily in divided doses, but some patients may require up to 60 mg daily.

In patients who have had a **myocardial infarction** timolol maleate is given in initial doses of 5 mg twice daily for 2 days, starting 7 to 28 days after infarction, and increased subsequently in the absence of any contra-indicating adverse effects, to 10 mg twice daily.

Doses of 10 to 20 mg daily of timolol maleate are used in the prophylaxis of **migraine**.

Reduced doses may be required in renal or hepatic impairment.

Preparations

BP 2008: Timolol Eye Drops; Timolol Tablets;
USP 31: Timolol Maleate and Hydrochlorothiazide Tablets; Timolol Maleate Ophthalmic Solution; Timolol Maleate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Glatim; Ingetim; Klonalol; Ofal; Plostim; Poentimol; Proflax; Protevis; Timed; Timoler; Timolpres; Timoptic; Zopirol; ***Austral.:*** Nyogel; Optimol†; Tenopt; Timoptol; Timoptol-XE; ***Austria:*** Blocadren; Dispatim; Ophtilan†; Tim-Ophtal; Timabak; Timax; Timo-COMOD; Timoftal; Timohexal; Timoptic; ***Belg.:*** Blocadren; Nyogel; Nyolol; Timabak; Timo-POS; Timoptol; Timoptolgel; ***Braz.:*** Glaucotrat; Glautimol; Nyolol; Tenoftal; Timabak; Timoptol; ***Canad.:*** Apo-Timol; Apo-Timop; Novo-Timol; Tim-Ak†; Timoptic; ***Chile:*** Glausolets; Nyolol; Timabak; Timop; Timoptol-XE; Tiof; ***Cz.:*** Arutimol; Oftan; Oftensin†; Ophthalmo-Timogal; Timo-COMOD; Timogal†; Timohexal; Timoptol; Uni Timolol; ***Denm.:*** Aquanil; Oftamolol; Optimol; Timacar; Timosan; ***Fin.:*** Aquanil†; Blocanol; Timosan; ***Fr.:*** Digaol; Nyogel; Ophtim; Timabak; Timacor; Timo-COMOD; Timoptol; ***Ger.:*** Arutimol; Chibro-Timoptol; Dispatim; Nyogel; Tim-Ophtal; Timo-COMOD; Timo-Stulln; TimoEDO; Timohexal; Timomann; Timosine†; ***Gr.:*** Flumetol†; Glafemak; Lithimole; Noval; Nyogel; Nyolol; Temserin; Thilotim; Timabak; Timodose†; Waucosin†; Yesan; ***Hong Kong:*** Apo-Timop; Glauco-Oph†; Nyolol; Oftan; Optimol; Timabak; Timoptol; ***Hung.:*** Arutimol; Cusimolol; Nyolol; Oftan Timolol; ***India:*** Glucomol; Glucotim; Ocupres; Ocutim; Timolo; ***Indon.:*** Isotic Adretor; Kentimol; Nyolol; Tim-Ophtal; Ximex Opticom; ***Irl.:*** Nyogel; Timoptol; ***Israel:*** Nyolol; Octil†; Tiloptic; V-Optic; ***Ital.:*** Blocadren; Cusimolol; Droptimol; Ialutim; Nyogel; Oftimolo; Timolabak; Timolux; Timoptol; Timosoft; ***Jpn:*** Timoptol; ***Malaysia:*** Cusimolol; Nyolol†; Timo-COMOD†; Timolast; Timoptol; ***Mex.:*** Blocadren; Horex; Imot; Jertz; Nyolol; Shemol; Timoptol; Timozzard; Tiof†; ***Mon.:*** Nyolol; ***Neth.:*** Loptomit†; Nyogel; Timo-COMOD; Timoptol; ***Norw.:*** Aquanil; Blocadren; Oftamolol; Oftan; Timosan; ***NZ:*** Apo-Timol; Apo-Timop; Gen-Timolol†; Hypermol; Nyogel†; Tilmat; Timolux; Timoptol; ***Philipp.:*** Elevex; Glocure-Opta; Nyolol; Oftan; Timabak; Timoptol; ***Pol.:*** Cusimolol; Nyolol; Oftan; Oftensin; Timo-COMOD; Timohexal; Timoptic; ***Port.:*** Blocadren†; Cusimolol†; Nyogel; Nyolol; Timabak; Timogel; Timoglau; Timolen; Timoptol; ***Rus.:*** Arutimol (Арутимол); Glymol (Глимол); Nyolol (Ниолол); Ocumed (Окумед); Ocupres-E (Окупрес-Е); Oftan Timolol (Офтан Тимолол); Optimol (Оптимол); Timohexal (Тимогексал); ***S.Afr.:*** Glaucosan; Nyogel; Timoptol; ***Singapore:*** Nyolol; Timabak; Timoptol; ***Spain:*** Cusimolol; Nyolol; Timabak; Timoftol; Timogel; ***Swed.:*** Aquanil†; Blocadren; Optimol; Timosan; ***Switz.:*** Nyolol; Oftan†; Timisol; Timo-COMOD; Timoptic; ***Thai.:*** Glauco-Oph; Nyolol; Oftan†; Timo-Optal; Timodrop; Timoptol; Timosil; ***Turk.:*** Cusimolol; Nyolol; Timo-COMOD; Timoftal; Timoptic; Timosol; ***UK:*** Betim; Glau-opt†; Nyogel; Timoptol; ***USA:*** Betimol; Blocadren; Isatol; Istalol; Timoptic; ***Venez.:*** Globitan; Imot†; Matigel; Matilol; Nyolol; Timoptol.

Multi-ingredient: ***Arg.:*** Combigan; Cosopt; Dorlamida T; Dorzoflax†; Glaucocin†; Glaucotensil; Glaucotensil TD; Louten T; Moducren†; Ocuprostim; Ofal P†; Pilotim; Timed 0.5; Timed D; Timpilo†; Xalacom; ***Austral.:*** Combigan; Cosopt; Timpilo; Xalacom; ***Austria:*** Cosopt; Fotil; Moducrin; Timpilo; Timsopt; Xalacom; ***Belg.:*** Cosopt; Xalacom; ***Braz.:*** Combigan; Cosopt; Xalacom; ***Canad.:*** Combigan; Cosopt; Timolide†; Timpilo†; Xalacom; ***Chile:*** Combigan; Cosopt; Dorsof T; Gaax T; Glaucotensil T; Glausolets Plus; Latof-T; Tiof Plus; Xalacom; ***Cz.:*** Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Timpilo†; Xalacom; ***Denm.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***Fin.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***Fr.:*** Cosopt; Moducren; Pilobloq; Timpilo†; Xalacom; ***Ger.:*** Cosopt; Fotil; Moducrin; Timpilo†; TP-Ophtal; Xalacom; ***Gr.:*** Combigan; Cosopt; Dropiltim; DuoTrav; Fotil†; Ganfort; T+P; Tesol†; Timpilo; Xalacom; Yvano; ***Hong Kong:*** Cosopt; Moducren; Timpilo; Xalacom; ***Hung.:*** Combigan; Cosopt; DuoTrav; Fotil; Xalacom; ***Indon.:*** Xalacom; ***Irl.:*** Combigan; Cosopt; Moducren; Xalacom; ***Israel:*** Cosopt; Timpilo; Xalacom; ***Ital.:*** Cosopt; Equiton; Glautimol; Pilobloc; Timicon; Xalacom; ***Malaysia:*** Cosopt; Timpilo†; Xalacom; ***Mex.:*** Combigan-D; Cosopt; Xalacom; ***Neth.:*** Cosopt; Fotil; Xalacom; ***Norw.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***NZ:*** Combigan; Cosopt; DuoTrav; Timpilo; Xalacom; ***Philipp.:*** Cosopt; Fotil; Xalacom; ***Pol.:*** Cosopt; DuoTrav; Fotil; Xalacom; ***Port.:*** Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Moducren†; Tavu; Timoglau Plus; Timosopt; Xalacom; ***Rus.:*** Fotil (Фотил); Xalacom (Ксалаком); ***S.Afr.:*** Cosopt; Moducren; Servatrin; Xalacom; ***Singapore:*** Cosopt; Timpilo†; Xalacom; ***Spain:*** Xalacom; ***Swed.:*** Cosopt; Fotil; Timpilo†; Xalcom; ***Switz.:*** Combigan; Cosopt; Fotil†; Moducren; Timpilo†; Xalacom; ***Thai.:*** Cosopt; Fotil†; Xalacom; ***Turk.:*** Cosopt; ***UK:*** Combigan; Cosopt; DuoTrav; Ganfort; Moducren†; Prestim; Xalacom; ***USA:*** Combigan; Cosopt; Timolide; ***Venez.:*** Cosopt; Dobet; Glaucotensil T; Xalacom.

Tinzaparin Sodium *(BAN, USAN, rINN)*

Tintsapariininatrium; Tinzaparin sodná sůl; Tinzaparin Sodyum; Tinzaparina sódica; Tinzaparine sodique; Tinzaparinnatrium; Tinzaparin-nátrium; Tinzaparino natrio druska; Tinzaparinum natricum.

Тинзапарин Натрий

CAS — 9041-08-1.

ATC — B01AB10.

ATC Vet — QB01AB10.

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

Ph. Eur. 6.2 (Tinzaparin Sodium). It is prepared by enzymatic depolymerisation, using heparinase from *Flavobacterium heparinum*, of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5500 and 7500, with a characteristic value of about 6500. The mass percentage of chains lower than 2000 is not more than 10%. The degree of sulfation is 1.8 to 2.5 per disaccharide unit.

The potency is not less than 70 units and not more than 120 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 1.5 and 2.5.

Units

As for Low-molecular-weight Heparins, p.1329.

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p.1329.

Severe bleeding with tinzaparin sodium may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of 100 units of tinzaparin sodium.

Interactions

As for Low-molecular-weight Heparins, p.1329.

Pharmacokinetics

Tinzaparin sodium is absorbed after subcutaneous injection with a bioavailability of about 90%. Peak plasma activity is reached within 4 to 6 hours. The elimination half-life is about 90 minutes but detectable anti-factor Xa activity persists for up to 24 hours.

Uses and Administration

Tinzaparin sodium is a low-molecular-weight heparin (p.1329) with anticoagulant properties. It is used in the prevention and treatment of venous thromboembolism (p.1189) and to prevent clotting during extracorporeal circulation.

For *prophylaxis* of **venous thromboembolism** tinzaparin sodium is given by subcutaneous injection in a variety of dosage regimens.

- For patients undergoing general surgical procedures 3500 units of tinzaparin sodium are given 2 hours before the procedure, followed by 3500 units once daily for 7 to 10 days.
- In patients at high risk, such as those undergoing orthopaedic surgery, a dose of 50 units/kg has been recommended; alternatively, a dose of 4500 units may be given 12 hours before surgery, followed by 4500 units once daily.

For the *treatment* of venous thromboembolism tinzaparin sodium is given in a dose of 175 units/kg by subcutaneous injection once daily for at least 6 days and until adequate oral anticoagulation is established.

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, tinzaparin sodium may be given into the arterial side of the dialyser or intravenously. The dialyser may be primed with 500 to 1000 mL sodium chloride 0.9% containing 5000 units tinzaparin sodium/litre. For dialysis sessions lasting less than 4 hours a single dose of 2000 to 2500 units tinzaparin sodium is given; for longer sessions an initial dose of 2500 units is followed by an infusion of 750 units/hour.

◊ References.

1. Friedel HA, Balfour JA. Tinzaparin: a review of its pharmacology and clinical potential in the prevention and treatment of thrombo-embolic disorders. *Drugs* 1994; **48:** 638–60.
2. Neely JL, *et al.* Tinzaparin sodium: a low-molecular-weight heparin. *Am J Health-Syst Pharm* 2002; **59:** 1426–36.
3. Nutescu EA, *et al.* Tinzaparin: considerations for use in clinical practice. *Ann Pharmacother* 2003; **37:** 1831–40.
4. Cheer SM, *et al.* Tinzaparin sodium: a review of its pharmacology and clinical use in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2004; **64:** 1479–502.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Innohep†; ***Belg.:*** Innohep; ***Canad.:*** Innohep; ***Denm.:*** Innohep; ***Fin.:*** Innohep†; ***Fr.:*** Innohep; ***Ger.:*** Innohep; ***Gr.:*** Innohep; ***Hong Kong:*** Innohep; ***Irl.:*** Innohep; ***Israel:*** Innohep†; ***Malaysia:*** Innohep; ***Neth.:*** Innohep; ***Norw.:*** Innohep; ***NZ:*** Innohep; ***Philipp.:*** Innohep; ***Port.:*** Innohep; ***Singapore:*** Innohep; ***Spain:*** Innohep; ***Swed.:*** Innohep; ***Thai.:*** Innohep; ***Turk.:*** Innohep; ***UK:*** Innohep; ***USA:*** Innohep.

Tioclomarol *(rINN)*

LM-550; Tioclomarolum. 3-[5-Chloro-α-(4-chloro-β-hydroxyphenethyl)-2-thenyl]-4-hydroxycoumarin.

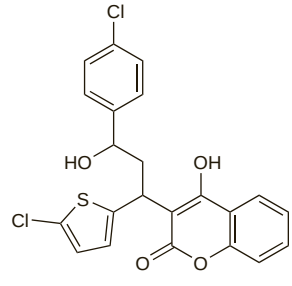
Тиокломарол

$C_{22}H_{16}Cl_2O_4S$ = 447.3.

CAS — 22619-35-8.

ATC — B01AA11.

ATC Vet — QB01AA11.



Profile

Tioclomarol is an oral coumarin anticoagulant with actions similar to those of warfarin (p.1425) that has been used in the management of thromboembolic disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Apegmone†.