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.

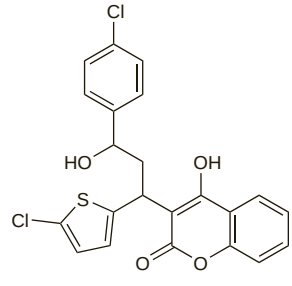
Тиокломарол

$C_{22}H_{16}Cl_2O_4S$ = 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†.