Tertatolol Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de tertatolol; S-2395 (tertatolol or tertatolol hydrochloride); SE-2395 (tertatolol or tertatolol hydrochloride); Tertatolol, Chlorhydrate de; Tertatololi Hydrochloridum. (±)-1-(*tert*-Butylamino)-3-(thiochroman-8-yloxy)propan-2-ol hydrochloride.

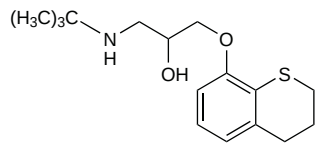
Тертатолола Гидрохлорид

$C_{16}H_{25}NO_2S,HCl$ = 331.9.

CAS — 34784-64-0 (tertatolol); 33580-30-2 (tertatolol hydrochloride).

ATC — C07AA16.

ATC Vet — QC07AA16.



(tertatolol)

Profile

Tertatolol is a non-cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity.

Tertatolol is given orally as the hydrochloride in the management of hypertension (p.1171) in a dose of 5 mg tertatolol hydrochloride once daily, increased to 10 mg once daily if required.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Artexal; ***Fr.:*** Artex; ***Irl.:*** Artexal; ***Neth.:*** Artex; ***Port.:*** Artex.

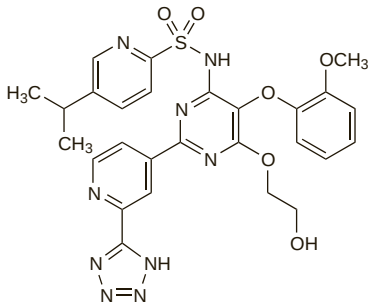
Tezosentan *(BAN, rINN)*

Tézosentan; Tezosentán; Tezosentanum. *N*-{6-(2-Hydroxyethoxy)-5-(*o*-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)-4-pyridyl]-4-pyrimidinyl}-5-isopropyl-2-pyridinesulfonamide.

Тезозентан

$C_{27}H_{27}N_9O_6S$ = 605.6.

CAS — 180384-57-0.



Profile

Tezosentan is an endothelin receptor antagonist that has been studied in acute heart failure.

◊ References.

1. Torre-Amione G, *et al.* Hemodynamic effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with class III to IV congestive heart failure. *Circulation* 2001; **103:** 973–80.
2. Tovar JM, Gums JG. Tezosentan in the treatment of acute heart failure. *Ann Pharmacother* 2003; **37:** 1877–83.
3. Cotter G, *et al.* The hemodynamic and neurohormonal effects of low doses of tezosentan (an endothelin A/B receptor antagonist) in patients with acute heart failure. *Eur J Heart Fail* 2004; **6:** 601–9.
4. McMurray JJV, *et al.* Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA* 2007; **298:** 2009–19.

Tiadenol *(rINN)*

LL-1558; Tiadénol; Tiadenolum. 2,2′-(Decamethylenedithio)diethanol.

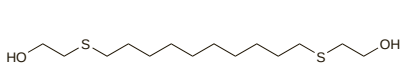
Тиаденол

$C_{14}H_{30}O_2S_2$ = 294.5.

CAS — 6964-20-1.

ATC — C10AX03.

ATC Vet — QC10AX03.



Profile

Tiadenol is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). The usual oral dose is 1.2 to 2.4 g daily in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Fonlipol.

Ticlopidine Hydrochloride

(BANM, USAN, rINNM)

4-C-32; 53-32C; Hidrocloruro de ticlopidina; Ticlopidine, chlorhydrate de; Ticlopidini hydrochloridum; Tiklopidiinihydrokloridi; Tiklopidin Hidroklorür; Tiklopidinhidroklorid; Tiklopidin-hydroklorid; Tiklopidinhydroklorid; Tiklopidino hidrochloridas. 5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride.

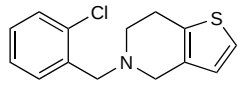
Тиклопидина Гидрохлорид

$C_{14}H_{14}ClNS,HCl$ = 300.2.

CAS — 55142-85-3 (ticlopidine); 53885-35-1 (ticlopidine hydrochloride).

ATC — B01AC05.

ATC Vet — QB01AC05.



(ticlopidine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Ticlopidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; very slightly soluble in ethyl acetate. A 2.5% solution in water has a pH of 3.5 to 4.0.

Adverse Effects and Precautions

Gastrointestinal disturbances, skin rashes, and bleeding are the most commonly reported adverse effects associated with ticlopidine therapy. Blood dyscrasias, including neutropenia, thrombotic thrombocytopenic purpura, and aplastic anaemia, have also occurred. There have been reports of hepatitis and cholestatic jaundice. Blood-lipid concentrations may increase during long-term therapy.

Ticlopidine should not be given to patients with haematopoietic disorders such as neutropenia or thrombocytopenia, haemorrhagic diathesis or other haemorrhagic disorders associated with a prolonged bleeding time, or conditions with an increased risk of bleeding such as peptic ulcer disease, acute cerebral haemorrhage, or severe liver dysfunction. Full blood counts should be performed before starting treatment and every 2 weeks during the first 3 months of therapy. If ticlopidine is stopped during this period, a full blood count should be performed within 2 weeks of stopping treatment. Consideration should be given to stopping ticlopidine therapy 10 to 14 days before elective surgery.

Effects on the blood. Severe *neutropenia* or *agranulocytosis* may occur in about 1% of patients given ticlopidine[1] and fatal infection has been reported.[2] Neutropenia usually develops within the first 3 months of therapy and is reversible on stopping ticlopidine, but there has been a report[3] of a delayed reaction that occurred 18 days after ticlopidine was stopped. Isolated *thrombocytopenia* occurs in about 0.4% of patients and *thrombotic thrombocytopenic purpura*, sometimes fatal, has occurred.[1,4-7] Conversely, good results have been achieved with ticlopidine as a treatment for thrombotic thrombocytopenic purpura,[8,9] but it should only be used with extreme caution.[10] Aplastic anaemia has also occurred rarely with ticlopidine.[1,11]

Clopidogrel has also been associated with blood dyscrasias. Up to August 2004, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[12] had received 80 reports of blood dyscrasias associated with clopidogrel, although ticlopidine was associated with a much higher rate of reports. Individual cases of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome,[13-16] aplastic anaemia,[17] leucopenia,[18] and acquired haemophilia A,[19] have also been reported. However the most frequently reported adverse effect of clopidogrel, as with other antithrombotics, is bleeding, particularly when given with other drugs affecting coagulation; ADRAC had received 130 reports of haemorrhagic events, leading to fatalities in 18 cases.[12]

1. Love BB, *et al.* Adverse haematological effects of ticlopidine: prevention, recognition and management. *Drug Safety* 1998; **19:** 89–98.
2. Carlson JA, Maesner JE. Fatal neutropenia and thrombocytopenia associated with ticlopidine. *Ann Pharmacother* 1994; **28:** 1236–8.
3. Farver DK, Hansen LA. Delayed neutropenia with ticlopidine. *Ann Pharmacother* 1994; **28:** 1344–6.
4. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. *Ann Intern Med* 1998; **128:** 541–4.
5. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura after stenting and ticlopidine. *Lancet* 1998; **352:** 1036–7.
6. Steinhubl SR, *et al.* Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. *JAMA* 1999; **281:** 806–10.
7. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. *Arch Intern Med* 1999; **159:** 2524–8.
8. Vianelli N, *et al.* Thrombotic thrombocytopenic purpura and ticlopidine. *Lancet* 1991; **337:** 1219.
9. Bobbio-Pallavicini E, *et al.* Antiplatelet agents in thrombotic thrombocytopenic purpura (TTP): results of a randomized multicenter trial by the Italian Cooperative Group for TTP. *Haematologica* 1997; **82:** 429–35.
10. Rock G, *et al.* Thrombotic thrombocytopenic purpura treatment in year 2000. *Haematologica* 2000; **85:** 410–19.
11. Symeonidis A, *et al.* Ticlopidine-induced aplastic anemia: two new case reports, review, and meta-analysis of 55 additional cases. *Am J Hematol* 2002; **71:** 24–32.
12. Adverse Drug Reactions Advisory Committee (ADRAC). Clopidogrel—haemorrhage and haematological disorders. *Aust Adverse Drug React Bull* 2004; **23:** 14–15. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0408.htm (accessed 17/08/05)
13. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000; **342:** 1773–7.
14. Oomen PHN, *et al.* Hemolytic uremic syndrome in a patient treated with clopidogrel. *Ann Intern Med* 2000; **132:** 1006.
15. Andersohn F, *et al.* Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome associated with clopidogrel: report of two new cases. Abstract: *Heart* 2004; **90:** e57. Full version: http://heart.bmjjournals.com/cgi/content/full/90/9/e57 (accessed 17/08/05)
16. von Mach M-A, *et al.* Subacute coronary stent thrombosis in a patient developing clopidogrel associated thrombotic thrombocytopenic purpura. Abstract: *Heart* 2005; **91:** e14. Full version: http://heart.bmjjournals.com/cgi/content/full/91/2/e14 (accessed 17/08/05)
17. Trivier J-M, *et al.* Fatal aplastic anaemia associated with clopidogrel. *Lancet* 2001; **357:** 446.
18. McCarthy MW, Kockler DR. Clopidogrel-associated leukopenia. *Ann Pharmacother* 2003; **37:** 216–19.
19. Haj M, *et al.* Acquired haemophilia A may be associated with clopidogrel. *BMJ* 2004; **329:** 323.

Effects on the gastrointestinal tract. Diarrhoea is a common adverse effect of ticlopidine therapy; it usually occurs during the first few months of therapy and resolves within 1 to 2 weeks without stopping therapy. However, there has been a report[1] of diarrhoea and weight loss of 2 months duration that first presented 2 years after ticlopidine was started; diarrhoea resolved when ticlopidine was withdrawn.

1. Mansoor GA, Aziz K. Delayed chronic diarrhea and weight loss possibly due to ticlopidine therapy. *Ann Pharmacother* 1997; **31:** 870–2.

Effects on the joints. Acute arthritis associated with a diffuse rash developed in a patient shortly after starting treatment with ticlopidine.[1] Both the rash and the arthritis resolved on withdrawal, and it was suggested that a hypersensitivity reaction might be involved. One case of polyarthritis and 3 cases of arthralgia associated with ticlopidine had been reported to the UK CSM up to March 2001. Two cases of acute arthritis have also been reported[2] with clopidogrel; symptoms developed 2 to 3 weeks after starting treatment and resolved after stopping.

1. Dakik HA, *et al.* Ticlopidine associated with acute arthritis. *BMJ* 2002; **324:** 27.
2. Garg A, *et al.* Clopidogrel associated with acute arthritis. *BMJ* 2000; **320:** 483.

Effects on the kidneys. A reversible deterioration in renal function has been reported in patients given ticlopidine after coronary stent implantation.[1,2] There has also been a report[3] of membranous nephropathy with nephrotic syndrome in a patient receiving clopidogrel.

1. Elsman P, Zijlstra F. Ticlopidine and renal function. *Lancet* 1996; **348:** 273–4.
2. Virdee M, *et al.* Ticlopidine and renal function. *Lancet* 1996; **348:** 1031–2.
3. Tholl U, *et al.* Clopidogrel and membranous nephropathy. *Lancet* 1999; **354:** 1443–4.

Effects on the liver. Cholestatic hepatitis has been reported in patients receiving ticlopidine and is usually reversible when ticlopidine is stopped.[1-3] However, there have been reports of persistent cholestasis after ticlopidine withdrawal.[4,5] A case of granulomatous hepatitis has also been reported.[6] Clopidogrel was substituted for ticlopidine in a patient who had developed raised liver enzymes during ticlopidine treatment;[7] liver enzyme values returned to normal during continued clopidogrel therapy. However, there has been a report[8] of hepatotoxicity with clopidogrel.

1. Cassidy LJ, *et al.* Probable ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 1995; **29:** 30–2.
2. Pérez-Balsa AM, *et al.* Hepatotoxicity due to ticlopidine. *Ann Pharmacother* 1998; **32:** 1250–1.
3. Skurnik YD, *et al.* Ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 2003; **37:** 371–5.

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†.

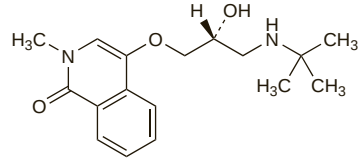
Tilisolol Hydrochloride *(rINNM)* ⊗

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.

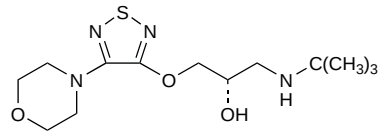
Тимолола Малеат

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