## 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.

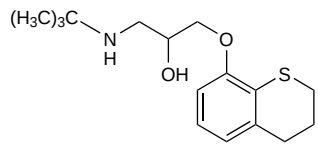
Тертатолола Гидрохлорид

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

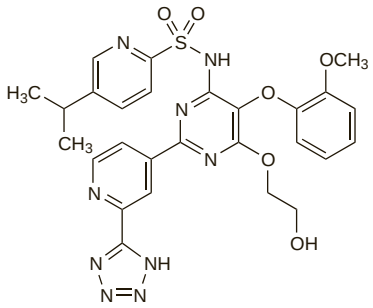
## Tezosentan *(BAN, rINN)*

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.

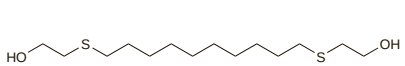
Тиаденол

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

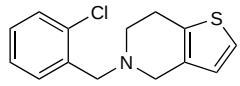
Тиклопидина Гидрохлорид

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