### Tirilazad Mesilate *(BANM, rINNM)*

Mesilato de tirilazad; Tirilatsadiinimesilaatti; Tirilazad, Mésilate de; Tirilazad Mesylate *(USAN)*; Tirilazadi Mesilas; Tirilazadini Mesilas; Tirilazadinmesilat; U-74006F (tirilazad or tirilazad mesilate). 21-[4-(2,6-Di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione monomethanesulfonate hydrate.

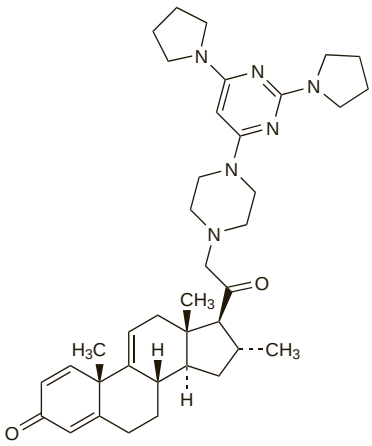
Тирилазада Мезилат

$C_{38}H_{52}N_6O_2,CH_4O_3S,xH_2O$ = 721.0 (anhydrous).

*CAS — 110101-66-1 (tirilazad); 111793-42-1 (tirilazad mesilate); 149042-61-5 (tirilazad mesilate).*

*ATC — N07XX01.*

*ATC Vet — QN07XX01.*



*(tirilazad)*

#### Profile

Tirilazad, a lazaroid, is an inhibitor of lipid peroxidation thought to have a cytoprotective effect against radicals produced in response to tissue trauma. It has been used in the prevention of secondary tissue damage in subarachnoid haemorrhage. It has also been investigated in spinal cord injuries, head injuries, and ischaemic stroke.

◊ References.


1. Fleishaker JC, *et al.* Evaluation of the pharmacokinetics and tolerability of tirilazad mesylate, a 21-aminosteroid free radical scavenger: multiple-dose administration. *J Clin Pharmacol* 1993; **33:** 182–90.
2. Hulst LK, *et al.* Effect of age and gender on tirilazad pharmacokinetics in humans. *Clin Pharmacol Ther* 1994; **55:** 378–84.
3. Haley EC, *et al.* Phase II trial of tirilazad in aneurysmal subarachnoid haemorrhage: a report of the Cooperative Aneurysm Study. *J Neurosurg* 1995; **82:** 786–90.
4. Clark WM, *et al.* Lazaroids: CNS pharmacology and current research. *Drugs* 1995; **50:** 971–83.
5. Marshall LF, *et al.* A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. *J Neurosurg* 1998; **89:** 519–25.
6. Fleishaker JC, *et al.* Hormonal effects on tirilazad clearance in women: assessment of the role of CYP3A. *J Clin Pharmacol* 1999; **39:** 260–7.
7. The Tirilazad International Steering Committee. Tirilazad for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/06/05).


#### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Austria:*** Freedox†; ***Belg.:*** Freedox†; ***S.Afr.:*** Freedox†; ***Switz.:*** Freedox†.

## Tirofiban Hydrochloride

*(BANM, USAN, rINNM)*

Hidrocloruro de tirofibán; L-700462; MK-383; MK-0383; Tirofiban, Chlorhydrate de; Tirofiban Hidroklorür; Tirofibani Hydrochloridum. *N*-(Butylsulfonyl)-4-[4-(4-piperidyl)butoxy]-L-phenylalanine hydrochloride monohydrate.

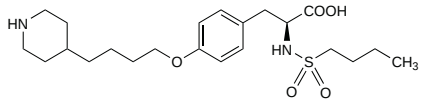
Тирофибана Гидрохлорид

$C_{22}H_{36}N_2O_5S,HCl,H_2O$ = 495.1.

*CAS — 144494-65-5 (tirofiban); 142373-60-2 (anhydrous tirofiban hydrochloride); 150915-40-5 (tirofiban hydrochloride monohydrate);.*

*ATC — B01AC17.*

*ATC Vet — QB01AC17.*



*(tirofiban)*

### Adverse Effects

Bleeding is the most common adverse effect of tirofiban. Other side-effects include nausea, headache, fever, rashes and other hypersensitivity reactions, and thrombocytopenia.

**Effects on the blood.** References[1,2] to tirofiban-associated thrombocytopenia.


1. Mulot A, *et al.* Practical approach to the diagnosis and management of thrombocytopenia associated with tirofiban treatment. *Am J Hematol* 2004; **77:** 67–71.
2. Patel S, *et al.* Profound thrombocytopenia associated with tirofiban: case report and review of literature. *Angiology* 2005; **56:** 351–5.


### Precautions

As for Abciximab, p.1192.

### Pharmacokinetics

After stopping an infusion of tirofiban, the antiplatelet effect persists for about 4 to 8 hours. The plasma half-life is about 2 hours. Tirofiban is not highly bound to plasma proteins; the unbound fraction in plasma is about 35%. Tirofiban is eliminated largely unchanged in the urine, with some biliary excretion in the faeces. Tirofiban is removed by haemodialysis.

◊ Reviews.


1. Kondo K, Umemura K. Clinical pharmacokinetics of tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist: comparison with the monoclonal antibody abciximab. *Clin Pharmacokinet* 2002; **41:** 187–95.


### Uses and Administration

Tirofiban hydrochloride is an antiplatelet drug that reversibly inhibits binding of fibrinogen to the glycoprotein IIb/IIIa receptors of platelets. It is given with heparin and aspirin for the management of unstable angina, both in patients managed medically and in those undergoing percutaneous coronary procedures. Tirofiban is used as the hydrochloride, but the dose is expressed in terms of the base; 110 nanograms of tirofiban hydrochloride monohydrate is equivalent to 100 nanograms of tirofiban base.

Tirofiban is given intravenously, at an initial rate of 400 nanograms/kg per minute for 30 minutes, and then continued at 100 nanograms/kg per minute. The recommended duration of treatment is at least 48 hours. Tirofiban infusion may be continued during coronary angiography, and should be maintained for 12 to 24 hours after angioplasty or atherectomy. The entire duration of treatment should not exceed 108 hours.

The dose of tirofiban should be reduced in patients with renal impairment (see below).

◊ General references.


1. McClellan KJ, Goa KL. Tirofiban: a review of its use in acute coronary syndromes. *Drugs* 1998; **56:** 1067–80.
2. Menozzi A, *et al.* Tirofiban in acute coronary syndromes. *Expert Rev Cardiovasc Ther* 2005; **3:** 193–206.
3. Shanmugam G. Tirofiban and emergency coronary surgery. *Eur J Cardiothorac Surg* 2005; **28:** 546–50.
4. Bukow SC, *et al.* Tirofiban for the treatment of ischaemic stroke. *Expert Opin Pharmacother* 2006; **7:** 73–9.
5. Mukherjee D, Roffi M. Current strategies with high-dose tirofiban. *Expert Opin Drug Metab Toxicol* 2007; **3:** 275–80.
6. Winter JP, Juergens CP. The role of tirofiban in the management of coronary artery disease. *Cardiovasc Hematol Disord Drug Targets* 2008; **8:** 138–46.


**Administration in renal impairment.** Patients with renal impairment (creatinine clearance less than 30 mL/minute) should receive half the usual infusion dose of tirofiban.

**Ischaemic heart disease.** Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. Tirofiban, given with heparin and aspirin, has been tried as adjunctive therapy. A study[1] comparing tirofiban with heparin in the **medical management** of unstable angina (p.1157) or non-Q-wave myocardial infarction reported an initial benefit, at 2 days, of reduced risk of refractory ischaemia, myocardial infarction, or death with tirofiban. This benefit was not maintained at 7 or 30 days after treatment, although a further analysis[2] found that the risk of death or myocardial infarction at 30 days was reduced in patients with raised troponin I concentrations who received tirofiban. In another study,[3] the combination of heparin and tirofiban also reduced the risk of refractory ischaemia, myocardial infarction, or death, compared with heparin alone, and benefit was maintained at 6 months. About half of these patients also underwent revascularisation procedures or surgery if required.

Tirofiban has also been studied in patients undergoing **interventional therapy** (see Reperfusion and Revascularisation Procedures, p.1181), but results have been mixed. The RESTORE trial[4] found short-term benefit with tirofiban as an adjunct to heparin in patients undergoing angioplasty or atherectomy for acute coronary syndromes (unstable angina or myocardial infarction), but this was not maintained at 30 days and there was no effect on restenosis after 6 months. However, another study using a higher loading dose found a reduced rate of clinical events in patients given tirofiban, both early after the procedure and on longer-term follow-up,[5] and an observational study[6] in patients with acute myocardial infarction also found improved outcomes. Pretreatment with tirofiban for 24 to 48 hours before intervention was found to improve angiographic outcomes compared with periprocedural treatment,[7] but there was no difference in clinical events at 30 days. In patients undergoing planned interventions, tirofiban was found to improve outcomes compared with placebo;[8] another study found that it was less effective than abciximab at 30 days,[9] although this difference was no longer apparent after 6 months.[10]


1. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; **338:** 1498–1505.
2. Heeschen C, *et al.* Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999; **354:** 1757–62.
3. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; **338:** 1488–97.
4. Gibson CM, *et al.* Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. *J Am Coll Cardiol* 1998; **32:** 28–34.
5. Valgimigli M, *et al.* The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004; **44:** 14–19.
6. De Luca G, *et al.* Impact of adjunctive tirofiban administration on myocardial perfusion and mortality in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. *Thromb Haemost* 2005; **93:** 820–3.
7. van 't Hof AWJ, *et al.* A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. *Eur Heart J* 2003; **24:** 1401–5.
8. Bonz AW, *et al.* Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol* 2002; **40:** 662–8.
9. Topol EJ, *et al.* Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001; **344:** 1888–94.
10. Moliterno DJ, *et al.* Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. *Lancet* 2002; **360:** 355–60.


#### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Agrastat; ***Austral.:*** Agrastat; ***Austria:*** Aggrastat; ***Belg.:*** Aggrastat; ***Braz.:*** Agrastat; ***Canad.:*** Aggrastat; ***Chile:*** Agrastat; ***Cz.:*** Aggrastat; ***Denm.:*** Aggrastat; ***Fin.:*** Aggrastat; ***Fr.:*** Agrastat; ***Ger.:*** Aggrastat; ***Gr.:*** Aggrastat; Avastar†; ***Hong Kong:*** Aggrastat; ***Hung.:*** Aggrastat; ***India:*** Aggribloc; ***Irl.:*** Aggrastat; ***Israel:*** Aggrastat; ***Ital.:*** Aggrastat; ***Malaysia:*** Aggrastat; ***Mex.:*** Agrastat; ***Neth.:*** Aggrastat; ***Norw.:*** Aggrastat; ***NZ:*** Aggrastat; ***Philipp.:*** Aggrastat; ***Pol.:*** Aggrastat; ***S.Afr.:*** Aggrastat; ***Singapore:*** Aggrastat; ***Spain:*** Agrastat; ***Swed.:*** Aggrastat; ***Switz.:*** Aggrastat; ***Thai.:*** Aggrastat; ***Turk.:*** Aggrastat; ***UK:*** Aggrastat; ***USA:*** Aggrastat; ***Venez.:*** Agrastat.

### Tocainide *(BAN, USAN, rINN)*

Tocainida; Tocaïnide; Tocainidum; Tokainid; Tokainidi; W-36095. 2-Aminopropiono-2',6'-xylidide.

Токаинид

$C_{11}H_{16}N_2O$ = 192.3.

*CAS — 41708-72-9.*

*ATC — C01BB03.*

*ATC Vet — QC01BB03.*