2. Oguchi H, *et al.* Pharmacokinetics of temocapril and enalapril in patients with various degrees of renal insufficiency. *Clin Pharmacokinet* 1993; **24:** 421–7.
3. Furuta S, *et al.* Pharmacokinetics of temocapril, an ACE inhibitor with preferential biliary excretion, in patients with impaired liver function. *Eur J Clin Pharmacol* 1993; **44:** 383–5.
4. Arakawa M, *et al.* Pharmacokinetics and pharmacodynamics of temocapril during repeated dosing in elderly hypertensive patients. *Eur J Clin Pharmacol* 2001; **56:** 775–9.
5. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; **41:** 207–24.
6. Yasunari K, *et al.* Pharmacological and clinical studies with temocapril, an angiotensin converting enzyme inhibitor that is excreted in the bile. *Cardiovasc Drug Rev* 2004; **22:** 189–98.

Preparations

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

Tenecteplase *(BAN, USAN, rINN)*

Tenecteplasa; Ténectéplase; Tenecteplasum; TNK-tPA. [103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanine]plasminogen activator (human tissue-type).

Тенектеплас

CAS — 191588-94-0.
ATC — B01AD11.
ATC Vet — QB01AD11.

Description. Tenecteplase is a 527 amino acid glycoprotein produced by recombinant DNA technology. It is a modified form of human tissue plasminogen activator.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p.1402

Interactions

As for Streptokinase, p.1404

Pharmacokinetics

After intravenous injection in patients with acute myocardial infarction, tenecteplase has a biphasic clearance from plasma with an initial half-life of 20 to 24 minutes and a terminal phase half-life of 90 to 130 minutes. It is cleared mainly by hepatic metabolism.

◊ Reviews.

1. Tanswell P, *et al.* Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clin Pharmacokinet* 2002; **41:** 1229–45.

Uses and Administration

Tenecteplase is a thrombolytic drug. It converts plasminogen to plasmin, a proteolytic enzyme that has fibrinolytic effects. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p.1045. Tenecteplase is a fibrin-specific thrombolytic (see p.1156).

Tenecteplase is used similarly to streptokinase (p.1404) in acute myocardial infarction (p.1175). It is given intravenously as a single bolus dose over 5 to 10 seconds as soon as possible after the onset of symptoms. The dose is based on body-weight and ranges from 30 mg in patients less than 60 kg to a maximum of 50 mg in those 90 kg or above.

◊ References.

1. Cannon CP, *et al.* TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation* 1998; **98:** 2805–14.
2. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; **354:** 716–22.
3. Llevadot J, *et al.* Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA* 2001; **286:** 442–9.
4. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; **358:** 605–13.
5. Turcasso NM, Nappi JM. Tenecteplase for treatment of acute myocardial infarction. *Ann Pharmacother* 2001; **35:** 1233–40.
6. Dunn CJ, Goa KL. Tenecteplase: a review of its pharmacology and therapeutic efficacy in patients with acute myocardial infarction. *Am J Cardiovasc Drugs* 2001; **1:** 51–66.
7. Melzer C, *et al.* Fibrinolysis of acute peripheral arterial occlusion with tenecteplase—a new weight-optimized treatment regimen. *J Thromb Thrombolysis* 2004; **18:** 43–6.
8. Spöhr F, *et al.* International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: the Thrombolysis in Cardiac Arrest (TROICA) Study. *Eur J Clin Invest* 2005; **35:** 315–23.
9. Kelly RV, *et al.* Safety of adjunctive intracoronary thrombolytic therapy during complex percutaneous coronary intervention: initial experience with intracoronary tenecteplase. *Catheter Cardiovasc Interv* 2005; **66:** 327–32.
10. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; **367:** 569–78.
11. Kline JA, *et al.* Tenecteplase to treat pulmonary embolism in the emergency department. *J Thromb Thrombolysis* 2007; **23:** 101–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Metalyse; ***Austria:*** Metalyse; ***Belg.:*** Metalyse; ***Braz.:*** Metalyse; ***Canad.:*** TNKase; ***Chile:*** Metalyse; ***Cz.:*** Metalyse; ***Denm.:*** Metalyse; ***Fin.:*** Metalyse; ***Fr.:*** Metalyse; ***Ger.:*** Metalyse; ***Gr.:*** Metalyse; ***Hong Kong:*** Metalyse; ***Hung.:*** Metalyse; ***Irl.:*** Metalyse; ***Ital.:*** Metalyse; ***Malaysia:*** Metalyse; ***Mex.:*** Metalyse; ***Neth.:*** Metalyse; ***Norw.:*** Metalyse; ***NZ:*** Metalyse; ***Pol.:*** Metalyse; ***Port.:*** Metalyse; ***Rus.:*** Metalyse (Метализе); ***S.Afr.:*** Metalyse; ***Spain:*** Metalyse; ***Swed.:*** Metalyse; ***Switz.:*** Metalyse; ***Thai.:*** Metalyse; ***UK:*** Metalyse; ***USA:*** TNKase.

Tenitramine

Tenitramina. *NNN′N′*-Tetrakis(2-hydroxyethyl)ethylenediamine tetranitrate.

$C_{10}H_{20}N_6O_{12}$ = 416.3.
CAS — 21946-79-2.
ATC — C01DA38.
ATC Vet — QC01DA38.

Profile

Tenitramine is a vasodilator with general properties similar to those of glyceryl trinitrate (p.1296) that has been used in angina pectoris (p.1157).

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Tenitran†.

Teprotide *(BAN, USAN, rINN)*

BPF_{9a}; L-Pyroglutamyl-L-tryptophyl-L-prolyl-L-arginyl-L-prolyl-L-glutaminyl-L-isoleucyl-L-prolyl-L-proline; SQ-20881; Teprotida; Téprotide; Teprotidum; 2-L-Tryptophan-3-de-L-leucine-4-de-L-proline-8-L-glutaminebradykinin potentiator B. 5-oxo-Pro-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro.

Тепротид

$C_{53}H_{76}N_{14}O_{12}$ = 1101.3.
CAS — 35115-60-7.

Profile

Teprotide is a nonapeptide originally found in the venom of *Bothrops jararaca*, a South American pit-viper. It is an ACE inhibitor with a short duration of action and has been given parenterally as an investigational tool.

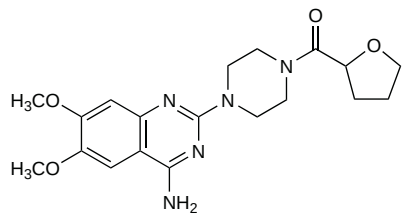
Terazosin Hydrochloride

(BANM, USAN, rINNM)

Abbott-45975; Hidrocloruro de terazosina; Teratsosiinihydrokloridi; Terazosin Hidroklorür; Térazosine, chlorhydrate de; Terazosinhydroklorid; Terazosini hydrochloridum. 1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(tetrahydro-2-furoyl)piperazine hydrochloride dihydrate; 6,7-Dimethoxy-2-[4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl]quinazolin-4-ylamine hydrochloride dihydrate.

Теразозина Гидрохлорид

$C_{19}H_{25}N_5O_4$,HCl,$2H_2O$ = 459.9.
CAS — 63590-64-7 (terazosin); 63074-08-8 (anhydrous terazosin hydrochloride); 70024-40-7 (terazosin hydrochloride dihydrate).
ATC — G04CA03.
ATC Vet — QG04CA03.



(terazosin)

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

Ph. Eur. 6.2 (Terazosin Hydrochloride Dihydrate). White or slightly yellow, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol; practically insoluble in acetone. A 2% solution in water has a pH of 3.0 to 5.0. Protect from light.

USP 31 (Terazosin Hydrochloride). A white to pale yellow, crystalline powder. soluble in water and in methyl alcohol; freely soluble in isotonic saline solution; slightly soluble in alcohol and in 0.1N hydrochloric acid; practically insoluble in acetone and in hexanes; very slightly soluble in chloroform. Store in airtight containers at a temperature between 20° and 25°.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375.

Urinary incontinence. For reference to urinary incontinence associated with terazosin, see under Adverse Effects of Prazosin Hydrochloride, p.1375.

Interactions

As for Prazosin Hydrochloride, p.1376.

Pharmacokinetics

Terazosin is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses; the bioavailability is reported to be about 90%. Peak plasma concentrations are achieved in about 1 hour. Terazosin is 90 to 94% protein bound. It is metabolised in the liver; one of the metabolites is reported to possess antihypertensive activity. The half-life in plasma is about 12 hours. Terazosin is excreted in faeces via the bile, and in the urine, as unchanged drug and metabolites.

Uses and Administration

Terazosin is an $alpha_1$-adrenoceptor blocker (p.1153) with actions similar to those of prazosin (p.1376), but a longer duration of action.

It is used in the management of hypertension (p.1171) and in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction.

Terazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Terazosin hydrochloride 1.2 mg is equivalent to about 1 mg of terazosin. After oral doses its hypotensive effects are seen within 15 minutes and may last for up to 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose the initial dose for both hypertension and benign prostatic hyperplasia is 1 mg of terazosin at bedtime, increasing gradually at intervals of 7 days according to the patient's response. For **hypertension** the usual maintenance dose is 2 to 10 mg once daily and the usual maximum dose is 20 mg daily in a single dose or two divided doses. For **benign prostatic hyperplasia** the usual maintenance dose is 5 to 10 mg once daily.

◊ Reviews.

1. Titmarsh S, Monk JP. Terazosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. *Drugs* 1987; **33:** 461–77.
2. Achari R, Laddu A. Terazosin: a new alpha adrenoceptor blocking drug. *J Clin Pharmacol* 1992; **32:** 520–3.
3. Wilt TJ, *et al.* Terazosin for benign prostatic hyperplasia. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 01/02/06).

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Andrin; Benaprost; Blavin; Eglidon; Flumarc; Fosfomik; Geriprost; Isontyn; Panaprost; Proxatan; Rotiaz; ***Austral.:*** Hytrin; ***Austria:*** Urocard; Uroflo; Vicard; ***Belg.:*** Hytrin; Terazosabb; Uro-Hytrin; ***Braz.:*** Hytrin; ***Canad.:*** Hytrin; ***Chile:*** Adecur; Hytrin; ***Cz.:*** Hytrin; Kornam; ***Denm.:*** Sinalfa; ***Fr.:*** Dysalfa; Hytrine; ***Ger.:*** Flotrin; Heitrin; Tera; Terablock; Teranar; Terazid; Terazoflo; ***Gr.:*** Hytrin; Vlanodrin; ***Hong Kong:*** Hytrin; ***Hung.:*** Hyron†; Hytrin; Kornam†; Setegis; ***India:*** Hytrin; Olyster; Zytrin; ***Indon.:*** Hytrin; ***Irl.:*** Benph; Hytrin; ***Israel:*** Hytrin; ***Ital.:*** Ezosina; Ibiprovir†; Itrin; Prostatil; Terafluss; Teraprost; Unoprost; Urodie; ***Malaysia:*** Hytrin; Terasin; ***Mex.:*** Adecur; Hytrin; Romaken; ***Neth.:*** Hytrin; ***Norw.:*** Sinalfa; ***NZ:*** Hytrin; ***Philipp.:*** Conmy; Hytrin; Lotencin; ***Pol.:*** Hytrin; Kornam; Setegis; Tesin; ***Port.:*** Hytrin; ***Rus.:*** Hytrin (Хитрин)†; Kornam (Корнам); Setegis (Сетегис); ***S.Afr.:*** Hytrin; ***Singapore:*** Hytrin; ***Spain:*** Alfaprost; Deflox; Magnurol; Mayul; Sutif; Tazusin†; Teraumon; Zayasel; ***Swed.:*** Hytrinex; Sinalfa; ***Switz.:*** Hytrin BPH; ***Thai.:*** Hytrin; ***Turk.:*** Hytrin; ***UK:*** Hytrin; ***USA:*** Hytrin; ***Venez.:*** Adecur; Hytrin.

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.

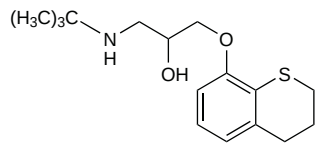
Тертатолола Гидрохлорид

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

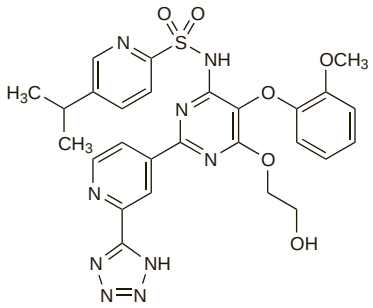
Tezosentan *(BAN, rINN)*

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.

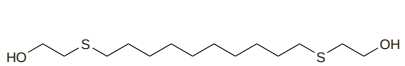
Тиаденол

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

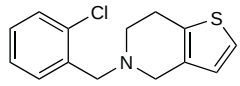
Тиклопидина Гидрохлорид

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