should be reserved for second-line treatment under close medical supervision in those who experience severe agitation and anxiety when stopping smoking.

Some individual studies have found clonidine to be more effective in women although the authors of the systematic review[1] recommended that these results be interpreted cautiously since some studies also found that women were less successful in giving up smoking unaided than men; treatment with clonidine, however, resulted in similar success rates in both men and women.

1. Gourlay SG, *et al.* Clonidine for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 26/09/05).

Tourette's syndrome. Clonidine is one of many drugs that have been tried in the management of Tourette's syndrome (see Tics, p.954).

Disturbance of monoamine metabolism (including dopamine, noradrenaline, and serotonin) has been implicated in Tourette's syndrome. Clonidine is thought to reduce central noradrenergic activity and may also affect other neurochemical systems, and these properties may account for its beneficial effects in this disorder. Studies of clonidine in Tourette's syndrome have produced mixed results,[1-5] although this may reflect the difficulty in study design for a disease that can vary considerably in severity and presence of comorbid conditions and whose symptoms wax and wane. A retrospective study[6] in juvenile patients given clonidine suggested that those showing improvement in the attention deficit hyperactivity disorder associated with Tourette's syndrome had previously had a longer duration of vocal tics; older children had a better overall response than younger children, who tended to suffer more from clonidine-induced drowsiness. However, no predictors of response could be identified. Nevertheless, clonidine is increasingly favoured for first-line treatment in patients with mild to moderate symptoms, because of a relative lack of serious adverse effects when compared to the commonly used antipsychotics pimozide and haloperidol, although exacerbation of tics and a marked sensation of heat have been reported[7] in one patient. Clonidine has also been reported to successfully control symptoms in some children with Tourette's syndrome unresponsive to haloperidol.[1]

Clonidine has also been used with stimulants in children with Tourette's syndrome and attention deficit hyperactivity disorder, although there have been concerns about the toxicity of such combinations (see Hyperactivity, above).

1. Cohen DJ, *et al.* Clonidine in Tourette's syndrome. *Lancet* 1979; **ii:** 551–3.
2. Shapiro AK, *et al.* Treatment of Gilles de la Tourette's syndrome with clonidine and neuroleptics. *Arch Gen Psychiatry* 1983; **40:** 1235–40.
3. Leckman JF, *et al.* Short- and long-term treatment of Tourette's syndrome with clonidine: a clinical perspective. *Neurology* 1985; **35:** 343–51.
4. Goetz CG, *et al.* Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. *Ann Neurol* 1987; **21:** 307–10.
5. Leckman JF, *et al.* Clonidine treatment of Gilles de la Tourette's syndrome. *Arch Gen Psychiatry* 1991; **48:** 324–8.
6. Lichter DG, Jackson LA. Predictors of clonidine response in Tourette syndrome: implications and inferences. *J Child Neurol* 1996; **11:** 93–7.
7. Kessler AR. Clonidine treatment increases tics in patients with Tourette syndrome: case report. *J Child Neurol* 2001; **16:** 380–1.

Preparations

BP 2008: Clonidine Injection; Clonidine Tablets;
USP 31: Clonidine Hydrochloride and Chlorthalidone Tablets; Clonidine Hydrochloride Tablets; Clonidine Transdermal System.

Proprietary Preparations (details are given in Part 3)
Arg.: Clonidural; ***Austral.:*** Catapres; ***Austria:*** Catapresan; Isoglaucon; ***Belg.:*** Catapressan; Dixarit; ***Braz.:*** Atensina; Clonesina†; Neo Clodil†; ***Canad.:*** Catapres; Dixarit; ***Chile:*** Catapresan; ***Cz.:*** Aruclonin; Catapresan; ***Denm.:*** Catapresan; ***Fin.:*** Catapresan; ***Fr.:*** Catapressan; ***Ger.:*** Aruclonin†; Catapresan; Clonid-Ophtal; Clonistada; Dispaclonidin; Dixarit†; Haemiton†; Isoglaucon; Mirfat†; Paracefan; ***Gr.:*** Catapresan; ***Hong Kong:*** Catapres†; Dixarit; ***Hung.:*** Aruclonin; ***India:*** Arkamin; Catapres; ***Indon.:*** Catapres; ***Irl.:*** Catapres; Dixarit; ***Israel:*** Clonnirit; Normopresan; ***Ital.:*** Adesipress-TTS†; Catapresan; Isoglaucon; ***Jpn:*** Catapres; ***Malaysia:*** Dixarit†; ***Mex.:*** Catapresan; Epiclodina; ***Neth.:*** Catapresan; Dixarit; ***Norw.:*** Catapresan; ***NZ:*** Catapres; Dixarit; ***Philipp.:*** Catapres; ***Pol.:*** Iporel; ***Port.:*** Catapresan; Edolglau; ***Rus.:*** Haemiton (Гемитон); ***S.Afr.:*** Dixarit; Menograine; ***Singapore:*** Dixarit†; ***Spain:*** Catapresan; Isoglaucon; ***Swed.:*** Catapresan; ***Switz.:*** Catapresan; ***Thai.:*** Catapres; Hypodine; ***UK:*** Catapres; Dixarit; ***USA:*** Catapres; Duraclon; ***Venez.:*** Catapresan; Clonipres†; Lowpres; Naclodin; Velaril.

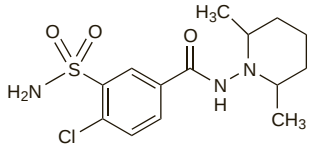
Multi-ingredient: ***Arg.:*** Bemplas; Pertenso; ***Ger.:*** Combipresan†; Haemiton compositum†; ***India:*** Arkamin-H; Catapres Diu; ***USA:*** Clorpres; Combipres†.

Clopamide *(BAN, USAN, rINN)* ⊗

Clopamida; Clopamidum; DT-327; Klopamid; Klopamidi. 4-Chloro-*N*-(2,6-dimethylpiperidino)-3-sulphamoylbenzamide; *cis*-3-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethyl-1-piperidinyl)benzamide.

Клопамид

$C_{14}H_{20}ClN_3O_3S$ = 345.8.
CAS — 636-54-4.
ATC — C03BA03.
ATC Vet — QC03BA03.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Clopamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water and in anhydrous alcohol; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Clopamide is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307) even though it does not contain a thiazide ring system. It is used for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis starts in 1 to 2 hours after an oral dose, reaches a maximum in about 3 to 6 hours, and lasts for up to 24 hours.

In the treatment of oedema the usual oral dose is 10 to 20 mg daily or on alternate days. For hypertension doses of 5 to 10 mg daily, either alone, or with other antihypertensives have been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Denm.: Adurix; ***Ger.:*** Brinaldix†; ***Hung.:*** Brinaldix; ***India:*** Brinaldix.

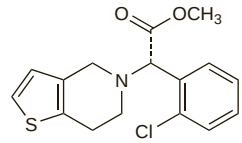
Multi-ingredient: ***Austria:*** Brinerdin; ***Belg.:*** Viskaldix; ***Braz.:*** Viskaldix; ***Chile:*** Viskaldix; ***Cz.:*** Crystepin; ***Fr.:*** Viskaldix; ***Ger.:*** Briserin N; Viskaldix; ***Gr.:*** Viskaldix; ***Hung.:*** Viskaldix; ***Irl.:*** Viskaldix; ***Ital.:*** Brinerdina; ***Malaysia:*** Viskaldix; ***Neth.:*** Viskaldix; ***Philipp.:*** Viskaldix; ***Pol.:*** Normatens; ***Port.:*** Brinerdine†; ***Rus.:*** Crystepin (Кристепин); Viskaldix (Вискалдикс); ***S.Afr.:*** Brinerdin; ***Spain:*** Brinerdina†; ***Switz.:*** Brinerdine; Viskaldix; ***Thai.:*** Bedin; Brinerdin; Hyperdine†; Viskaldix†; ***UK:*** Viskaldix; ***Venez.:*** Viskaldix†.

Clopidogrel Bisulfate *(USAN, rINNM)*

Bisulfato de clopidogrel; Clopidogrel, Bisulfate de; Clopidogrel Bisulphate *(BANM)*; Clopidogrel Hydrogen Sulphate; Clopidogreli Bisulfas; PCR-4099 (clopidogrel); SR-25990C. Methyl (*S*)-2-chlorophenyl(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)acetate bisulphate; Methyl (+)-(*S*)-α-(*o*-chlorophenyl)-6,7-dihydrothieno-[3,2-*c*]pyridine-5(4*H*)-acetate sulphate.

Клопидогрела Бисульфат

$C_{16}H_{16}ClNO_2S,H_2SO_4$ = 419.9.
CAS — 113665-84-2 (clopidogrel); 94188-84-8 (clopidogrel); 120202-66-6 (clopidogrel bisulfate).
ATC — B01AC04.
ATC Vet — QB01AC04.



(clopidogrel)

Pharmacopoeias. In *US.*
USP 31 (Clopidogrel Bisulfate). A white to off-white powder. Freely soluble in water and in methyl alcohol; practically insoluble in ether.

Adverse Effects and Precautions

As for Ticlopidine, p.1411.

The incidence of adverse effects, particularly blood dyscrasias, is lower with clopidogrel, although fatalities have been reported (see Effects on the Blood, p.1411). Routine blood counts are not necessary, although they should be performed promptly when clinical signs suggest blood dyscrasias. Other adverse effects, reported rarely, include serum sickness, interstitial pneumonitis, erythema multiforme, Stevens-Johnson syndrome, lichen planus, and myalgia.

Consideration should be given to stopping clopidogrel 5 to 7 days before elective surgery.

Effects on the blood. For reports of blood dyscrasias associated with clopidogrel therapy see under Adverse Effects of Ticlopidine, p.1411.

Effects on taste. Loss of taste occurred in 2 patients 6 to 8 weeks after starting treatment with clopidogrel, but recovered fully when clopidogrel was withdrawn.[1] Rechallenge in 1 of the patients led to recurrence of the taste loss, which persisted when treatment was stopped.

1. Golka K, *et al.* Reversible ageusia as an effect of clopidogrel treatment. *Lancet* 2000; **355:** 465–6.

Hypersensitivity. Clopidogrel has been associated with hypersensitivity reactions including angioedema.[1] There have also been reports[2-5] of a hypersensitivity syndrome comprising fever, rash, and varying additional symptoms.

1. Fischer TC, *et al.* Clopidogrel-associated angioedema. *Am J Med* 2003; **114:** 77–8.
2. Sarrot-Reynauld F, *et al.* Severe hypersensitivity associated with clopidogrel. *Ann Intern Med* 2001; **135:** 305–6.
3. Phillips EJ, *et al.* Serum sickness-like reaction associated with clopidogrel. *Br J Clin Pharmacol* 2003; **56:** 583.
4. Wolf I, *et al.* Clopidogrel-induced systemic inflammatory response syndrome. *Mayo Clin Proc* 2003; **78:** 618–20.
5. Doogue MP, *et al.* Clopidogrel hypersensitivity syndrome with rash, fever, and neutropenia. *Mayo Clin Proc* 2005; **80:** 1368–70.

Resistance. Results from platelet aggregation studies suggest that there is considerable variation in response to clopidogrel, although the clinical relevance of a low response (clopidogrel resistance) is unclear.[1,2] There is some evidence that the risk of cardiovascular events is higher in patients with clopidogrel resistance,[3] but this is not established. Factors that may contribute to clopidogrel resistance include drug interactions and genetic variation in platelet sensitivity or clopidogrel metabolism.[1,2] Patients with diabetes mellitus also appear to have a lower response.[4]

1. Nguyen TA, *et al.* Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005; **45:** 1157–64.
2. Angiolillo DJ, *et al.* Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007; **49:** 1505–16.
3. Geisler T, *et al.* Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation. *Eur Heart J* 2006; **27:** 2420–5.
4. Geisler T, *et al.* Platelet response to clopidogrel is attenuated in diabetic patients undergoing coronary stent implantation. *Diabetes Care* 2007; **30:** 372–4.

Interactions

Clopidogrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelets, and NSAIDs. Clopidogrel may inhibit the cytochrome P450 isoenzyme CYP2C9 and interactions with drugs metabolised by this isoenzyme are theoretically possible; it may also inhibit CYP2B6 (see Bupropion, below).

Antifungals. A study[1] in healthy subjects found that *ketoconazole* decreased the plasma concentration of the active metabolite of clopidogrel; platelet inhibitory action was also reduced.

1. Farid NA, *et al.* Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007; **81:** 735–41.

Bupropion. A study[1] in healthy subjects found that clopidogrel reduced the conversion of bupropion to its active metabolite, suggesting that clopidogrel inhibits the cytochrome P450 isoenzyme CYP2B6.

1. Turpeinen M, *et al.* Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. *Clin Pharmacol Ther* 2005; **77:** 553–9.

Ciclosporin. For reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin, see Statins, below.

Statins. There have been reports of rhabdomyolysis developing in patients when given clopidogrel in addition to ciclosporin and a statin (atorvastatin[1,2], lovastatin[3], or simvastatin[3]). Rhabdomyolysis is a recognised adverse effect when ciclosporin and statins are used together (see Immunosuppressants under Interactions of Simvastatin, p.1393), but the patients in these reports had previously received the combination without incident and developed rhabdomyolysis 1 to 3 weeks after clopidogrel was started. It has been suggested[2] that the mechanism is a three way interaction involving competition for binding sites on the cytochrome P450 isoenzyme CYP3A4 between statins and clopidogrel, exacerbated by ciclosporin-mediated enzyme inhibition.

Although it has been suggested that statins may decrease the antiplatelet effect of clopidogrel, evidence for such an interaction is conflicting and the clinical relevance has not been established.[4]

1. Anon. Clopidogrel (Plavix): suspected drug interaction with atorvastatin (Lipitor) and cyclosporine resulting in rhabdomyolysis. *Can Adverse React News* 2005; **15** (Apr): 3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n2_e.pdf (accessed 01/09/05)
2. Burton JR, *et al.* Clopidogrel-precipitated rhabdomyolysis in a stable heart transplant patient. *Ann Pharmacother* 2007; **41:** 133–7.
3. Uber PA, *et al.* Clopidogrel and rhabdomyolysis after heart transplantation. *J Heart Lung Transplant* 2003; **22:** 107–8.
4. Tafreshi MJ, *et al.* Combination of clopidogrel and statins: a hypothetical interaction or therapeutic dilemma? *Pharmacotherapy* 2006; **26:** 388–94.

Pharmacokinetics

Clopidogrel is rapidly but incompletely absorbed after oral doses; absorption appears to be at least 50%. It is a prodrug and is extensively metabolised in the liver, mainly to the inactive carboxylic acid derivative; metabolism is mediated by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, and to a lesser extent by CYP1A2, CYP1A1, and CYP2C19. The active metabolite appears to be a thiol derivative; it has been identified *in vitro* but appears to be too unstable to be isolated from plasma. Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in urine and in faeces; about 50% of an oral dose is recovered from the urine and about 46% from the faeces.

Uses and Administration

Clopidogrel is a thienopyridine antiplatelet drug used in thromboembolic disorders. It is an analogue of ticlopidine (p.1411) and acts by inhibiting adenosine diphosphate-mediated platelet aggregation. It is given prophylactically as an alternative to aspirin in patients with atherosclerosis who are at risk of thromboembolic disorders such as myocardial infarction (p.1175), peripheral arterial disease (p.1178), and stroke (p.1185). Clopidogrel is also used with aspirin in acute coronary syndromes, including acute myocardial infarction and unstable angina (p.1157), and in coronary stenting (see Reperfusion and Revascularisation Procedures, below).

Clopidogrel is given orally as the bisulfate, but doses are expressed in terms of the base; 97.86 mg of clopidogrel bisulfate is equivalent to 75 mg of base.

For the **prophylaxis of thromboembolic events**, the usual dose of clopidogrel is 75 mg once daily.

In the management of **acute ST-elevation myocardial infarction**, clopidogrel is used with aspirin as an adjunct in medically-treated patients. It is given in a dose of 75 mg once daily; patients under 75 years of age may be given a loading dose of 300 mg. Treatment should be continued for at least 4 weeks.

In the management of **unstable angina** and **non-Q-wave myocardial infarction**, clopidogrel is used with aspirin as an adjunct to either medical or interventional treatment, including coronary stenting. A single loading dose of 300 mg is given, followed by 75 mg once daily.

◊ Reviews.

1. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; **129:** 394–405.
2. Jarvis B, Simpson K. Clopidogrel: a review of its use in the prevention of atherothrombosis. *Drugs* 2000; **60:** 347–77.
3. Solet DJ, *et al.* The role of adenosine 5′-diphosphate receptor blockade in patients with cardiovascular disease. *Am J Med* 2001; **111:** 45–53.
4. Zambahari R, *et al.* Clinical use of clopidogrel in acute coronary syndrome. *Int J Clin Pract* 2007; **61:** 473–81.
5. Eshaghian S, *et al.* Role of clopidogrel in managing atherothrombotic cardiovascular disease. *Ann Intern Med* 2007; **146:** 434–41.
6. Plosker GL, Lyseng-Williamson KA. Clopidogrel: a review of its use in the prevention of thrombosis. *Drugs* 2007; **67:** 613–46.

Administration in children. Clopidogrel is not licensed for paediatric use in either the UK or the USA, although it has been given to small numbers of patients.

A retrospective study[1] of the use of clopidogrel in 15 children aged from 6 weeks to 16 years, 14 of whom had congenital heart disease, found that it was safe and effective; nearly all of the children were also taking aspirin and/or anticoagulants, and severe bleeding was reported in only 1 of them. The usual dose ranged from 1 to 3 mg/kg once daily, although a dose of 6 mg/kg daily was tolerated when given in error to 1 patient. A cohort study[2] of the use of clopidogrel alone or with aspirin in 17 children aged 1.5 to 17 years with arterial ischaemic stroke found that a daily dose of 0.5 to 2.4 mg/kg (target dose 1 mg/kg) was well tolerated, although subdural haematomas developed in 2 patients who were also taking aspirin.

1. Finkelstein Y, *et al.* Clopidogrel use in children. *J Pediatr* 2005; **147:** 657–61.
2. Soman T, *et al.* The risks and safety of clopidogrel in pediatric arterial ischemic stroke. *Stroke* 2006; **37:** 1120–2.

Atherosclerotic disorders. The use of aspirin to reduce the risk of cardiovascular events in patients with atherosclerotic vascular disorders is well established. Clopidogrel may have a role as an alternative. The CAPRIE trial[1] compared clopidogrel with aspirin in 19 185 patients at risk of ischaemic events, and found that clopidogrel reduced the risk of ischaemic stroke, myocardial infarction, or death from vascular causes to a greater extent than aspirin, although the absolute difference was small.

In acute coronary syndromes, clopidogrel may provide benefit when used in addition to aspirin. In patients with *unstable angina or non-ST elevation myocardial infarction*, the CURE trial[2] found that the risk of cardiovascular death, myocardial infarction, or stroke was lower in patients treated with clopidogrel and aspirin, compared with those receiving aspirin alone. Clopidogrel was given in a loading dose of 300 mg, started within 24 hours of the onset of symptoms, followed by 75 mg daily for 3 to 12 months.

Similar results have been reported in patients with acute *ST-elevation myocardial infarction*. Clopidogrel given with aspirin and thrombolytic therapy improved the patency of the affected artery and reduced the incidence of ischaemic complications at 30 days,[3] while a further study[4] found that addition of clopidogrel to aspirin and standard therapy (including thrombolytics in over half of the patients) also reduced early mortality.

Use of clopidogrel with aspirin has also been studied in *ischaemic stroke* but any benefit appears to be outweighed by an increased risk of bleeding. In the MATCH study,[5] adding aspirin to clopidogrel did not reduce the incidence of vascular events compared with clopidogrel alone, but the risk of major or life-threatening bleeding was increased. Similarly, in the CHARISMA study in patients with *stable atherosclerotic disease or multiple risk factors*, addition of clopidogrel to aspirin had no significant effect on the incidence of cardiovascular events, but the risk of moderate to severe bleeding was increased.[6]

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; **348:** 1329–39.
2. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502. Correction. *ibid.*; 1716.
3. Sabatine MS, *et al.* for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352:** 1179–89.
4. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; **366:** 1607–21.
5. Diener H-C, *et al.* Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364:** 331–7.
6. Bhatt DL, *et al.* CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; **354:** 1706–17.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention (PCI) has an established role in the management of both acute and stable coronary disease (see p.1181). Adjunctive antiplatelet therapy is given to reduce the risk of thrombosis, both during and after the procedure; a regimen of clopidogrel with aspirin improves outcomes[1] and is now generally recommended,[2,3] particularly if coronary stents are used. Although ticlopidine with aspirin was used initially in patients receiving stents, clopidogrel appears to be as effective as ticlopidine[4,5] but has a lower risk of haematological toxicity and is now generally preferred. A randomised study (CLASSICS)[6] found that, in patients given long-term aspirin, clopidogrel in a dose of 75 mg daily for 28 days, with or without a 300-mg loading dose, was as effective as ticlopidine; it was also better tolerated.

Pretreatment with clopidogrel appears to be most effective, but the increased bleeding risk may be of concern if emergency surgery is required. Use of a 300-mg loading dose shortly before the procedure appears to be safe, but efficacy may be reduced if it is given less than 6 hours before the intervention, and there is some evidence that it needs to be given at least 15 hours before.[7] A higher dose of 600 mg may be effective if given at least 2 hours before PCI,[8,9] and has been recommended in patients undergoing PCI for non-ST elevation acute coronary syndromes.[2]

The duration of combination therapy depends on the clinical situation. For patients given bare-metal stents, clopidogrel in a dose of 75 mg daily is usually given with aspirin for 2 to 4 weeks, and aspirin is then continued indefinitely. In patients with drug-eluting stents, the risk of occlusion persists for longer and combination therapy is usually recommended for at least 3 to 6 months; there is some evidence[10-12] that extending the duration further may provide additional benefit, and treatment for 12 months or longer has been suggested.[3] Prolonged combination therapy may also be of benefit in patients undergoing PCI for unstable angina, whether or not they receive stents.[1]

1. Mehta SR, *et al.* Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358:** 527–33.
2. Harrington RA, *et al.* Antithrombotic therapy for non-ST-elevation acute coronary syndromes: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 670S–707S.
3. Becker RC, *et al.* The primary and secondary prevention of coronary artery disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 776S–814S.
4. Mishkel GJ, *et al.*. Clopidogrel as adjunctive antiplatelet therapy during coronary stenting. *J Am Coll Cardiol* 1999; **34:** 1884–90.
5. Berger PB. Clopidogrel versus ticlopidine after intracoronary stent placement. *J Am Coll Cardiol* 1999; **34:** 1891–4.
6. Bertrand ME, *et al.* Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000; **102:** 624–9.
7. Steinhubl SR, *et al.* The CREDO Investigators. Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. *J Am Coll Cardiol* 2006; **47:** 939–43.
8. Longstreth KL, Wertz JR. High-dose clopidogrel loading in percutaneous coronary intervention. *Ann Pharmacother* 2005; **39:** 918–22.
9. Hochholzer W, *et al.* Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. *Circulation* 2005; **111:** 2560–4.
10. Zimarino M, *et al.* Optimal duration of antiplatelet therapy in recipients of coronary drug-eluting stents. *Drugs* 2005; **65:** 725–32.
11. Steinhubl SR, *et al.* Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; **288:** 2411–20. Correction. *ibid.* 2003; **289:** 987.
12. Eisenstein EL, *et al.* Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007; **297:** 159–68.

Preparations

USP 31: Clopidogrel Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Antiplaq; Clodian; Clodrel†; Iscover; Nabratin; Nefazan; Plavix; Pleyar; Troken; ***Austral.:*** Iscover; Plavix; ***Austria:*** Plavix; ***Belg.:*** Plavix; ***Braz.:*** Iscover; Plavix; ***Canad.:*** Plavix; ***Chile:*** Artevil; Iskimil; Plavix; ***Cz.:*** Iscover; Plavix; ***Denm.:*** Plavix; ***Fin.:*** Plavix; ***Fr.:*** Plavix; ***Ger.:*** Iscover; Plavix; ***Gr.:*** Iscover; Plavix; ***Hong Kong:*** Plavix; ***Hung.:*** Plavix; ***India:*** Cloflow; Clopact; Clopivas; Clopod; Noklot; Plavix; ***Indon.:*** Plavix; ***Irl.:*** Plavix; ***Israel:*** Plavix; ***Ital.:*** Iscover†; Plavix; ***Malaysia:*** Plavix; ***Mex.:*** Iscover; Plavix; ***Neth.:*** Iscover; Plavix; ***Norw.:*** Plavix; ***NZ:*** Plavix; ***Philipp.:*** Plavix; ***Pol.:*** Areplex; Plavix; Zyllt; ***Port.:*** Iscover†; Plavix; ***Rus.:*** Plavix (Плавикс); Zillt (Зилт); ***S.Afr.:*** Plavix; ***Singapore:*** Plavix; ***Spain:*** Iscover; Plavix; ***Swed.:*** Plavix; ***Switz.:*** Plavix; ***Thai.:*** Plavix; ***Turk.:*** Plavix; ***UK:*** Plavix; ***USA:*** Plavix; ***Venez.:*** Plavix.

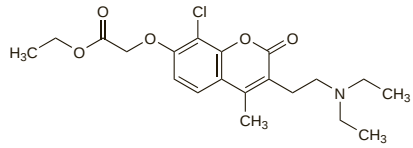
Multi-ingredient: ***Arg.:*** Nefazan Compuesto; ***India:*** Cloflow Plus†; Clopact A; Clopivas AP; Clopod-A.

Cloricromen *(rINN)*

Cloricromène; Cloricromeno; Cloricromenum. Ethyl ({8-chloro-3-[2-(diethylamino)ethyl]-4-methyl-2-oxo-2*H*-1-benzopyran-7-yl}oxy)acetate.

Клорикромен

$C_{20}H_{26}ClNO_5$ = 395.9.
CAS — 68206-94-0.
ATC — B01AC02.
ATC Vet — QB01AC02.



Profile

Cloricromen is an antiplatelet drug with vasodilating activity and is used in thromboembolic disorders (p.1187). It is given as the hydrochloride in arterial vascular disorders where there is a risk of thrombosis. It may be given orally in a dose of 100 mg two or three times daily or intravenously in a dose of 30 mg daily.

Preparations

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

Cloridarol *(rINN)*

Clobenfurol; Cloridarolum. α-(Benzofuran-2-yl)-α-(4-chlorophenyl)methanol.

Клоридарол

$C_{15}H_{11}ClO_2$ = 258.7.
CAS — 3611-72-1.
ATC — C01DX15.
ATC Vet — QC01DX15.