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.

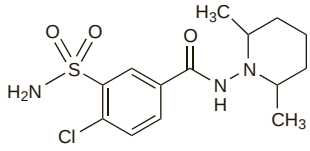
Multi-ingredient: ***Arg.:*** Bemplas; Pertenso; ***Ger.:*** Combipresan†; Haemiton compositum†; ***India:*** Arkamin-H; Catapres Diu; ***USA:*** Clorpres; Combipres†.

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.

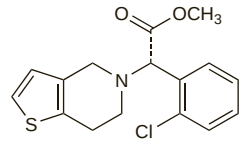
Multi-ingredient: ***Austria:*** Brinerdin; ***Belg.:*** Viskaldix; ***Braz.:*** Viskaldix; ***Chile:*** Viskaldix; ***Cz.:*** Crystepin; ***Fr.:*** Viskaldix; ***Ger.:*** Briserin N; Viskaldix; ***Gr.:*** Viskaldix; ***Hung.:*** Viskaldix; ***Irl.:*** Viskaldix; ***Ital.:*** Brinerdina; ***Malaysia:*** 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.