giozem†; Angitil; Calcicard; Dilcardia; Dilzem; Disogram; Optil; Slozem; Tildiem; Viazem; Zemtard; ***USA:*** Cardizem; Cartia; Dilacor; Dilt-CD; Dilt-XR; Diltia; Taztia; Tiazac; ***Venez.:*** Acalix; Corazem; Cordisil; Daltazen; Presoquin; Tilazem.

Multi-ingredient: ***Arg.:*** Lotrix†; ***USA:*** Teczem.

Dimetofrine Hydrochloride *(rINNM)* ⊗

Dimétofrine, Chlorhydrate de; Dimetofrini Hydrochloridum; Dimetophrine Hydrochloride; Hidrocloruro de dimetofrina. 4-Hydroxy-3,5-dimethoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride.

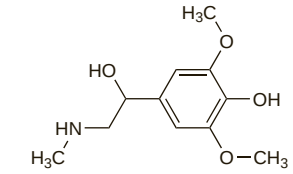
Диметофрина Гидрохлорид

$C_{11}H_{17}NO_4,HCl$ = 263.7.

CAS — 22950-29-4 (dimetofrine); 22775-12-8 (dimetofrine hydrochloride).

ATC — C01CA12.

ATC Vet — QC01CA12.



(dimetofrine)

Profile

Dimetofrine hydrochloride is a sympathomimetic (p.1407) that has been used for its vasopressor effects in the treatment of hypotensive states. It has also been used in preparations for cold and influenza symptoms.

Preparations

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

Multi-ingredient: ***Ital.:*** Raffreddoremed.

Dipyridamole *(BAN, USAN, rINN)*

Dipiridamol; Dipiridamolis; Dipirydamol; Dipyridamol; Dipyridamoli; Dipyridamolum; NSC-515776; RA-8. 2,2′,2″,2‴-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol.

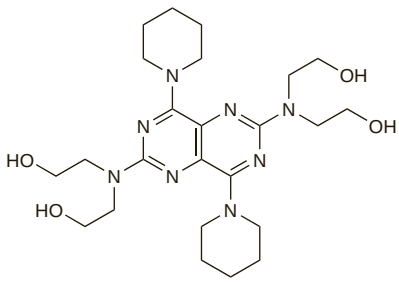
Дипиридамол

$C_{24}H_{40}N_8O_4$ = 504.6.

CAS — 58-32-2.

ATC — B01AC07.

ATC Vet — QB01AC07.



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

Ph. Eur. 6.2 (Dipyridamole). A bright yellow crystalline powder. Practically insoluble in water; soluble in dehydrated alcohol; freely soluble in acetone. It dissolves in dilute solutions of mineral acids. Protect from light.

USP 31 (Dipyridamole). An intensely yellow, crystalline powder or needles. Slightly soluble in water; very soluble in chloroform, in alcohol, and in methyl alcohol; very slightly soluble in acetone and in ethyl acetate. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Gastrointestinal disturbances, including nausea, vomiting, and diarrhoea, headache, dizziness, faintness, hypotension, facial flushing, and skin rash and other hypersensitivity reactions may occur after use of dipyridamole. Dipyridamole can also induce chest pain or lead to a worsening of the symptoms of angina. Cardiac arrhythmias have been reported in patients given dipyridamole during thallium-201 imaging. Aminophylline may reverse some of the adverse effects.

Dipyridamole should be used with caution in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, or coagulation disorders. Intravenous dipyridamole should not be given to patients with these conditions or to those with arrhythmias, conduction disorders, asthma, or a history of bronchospasm (but see Myocardial Imaging, below). Oral dipyridamole should be stopped 24 hours before intravenous use for stress testing.

Effects on the biliary tract. Gallstones containing unconjugated dipyridamole were removed from 2 patients who had been taking dipyridamole for 15 and 10 years, respectively.[1] A gallstone containing unconjugated dipyridamole recurred in a patient who continued to take the drug after endoscopic removal of a similar stone 18 months earlier.[2]

1. Moesch C, *et al.* Biliary drug lithiasis: dipyridamole gallstones. *Lancet* 1992; **340:** 1352–3.
2. Sautereau D, *et al.* Recurrence of biliary drug lithiasis due to dipyridamole. *Endoscopy* 1997; **29:** 421–3.

Effects on the heart. Transient myocardial ischaemia occurred in 4 patients with unstable angina and multivessel coronary artery disease during oral treatment with dipyridamole.[1] See Myocardial Imaging, below, for additional reports.

1. Keltz TN, *et al.* Dipyridamole-induced myocardial ischemia. *JAMA* 1987; **257:** 1515–16.

Effects on the muscles. Symptoms resembling acute pseudopolymyalgia rheumatica developed in a patient taking dipyridamole.[1]

1. Chassagne P, *et al.* Pseudopolymyalgia rheumatica with dipyridamole. *BMJ* 1990; **301:** 875.

Effects on taste. A disagreeable taste associated with other gastrointestinal symptoms occurred in a patient taking dipyridamole.[1] Two similar cases had been reported to the UK CSM.

1. Willoughby JMT. Drug-induced abnormalities of taste sensation. *Adverse Drug React Bull* 1983; **100:** 368–71.

Myocardial imaging. Dipyridamole may be used in association with thallium-201 in myocardial stress imaging. Safety data from over 3900 patients has been summarised.[1] Adverse effects which occurred within 24 hours of dipyridamole intravenously (mean dose 560 micrograms/kg) were recorded. Ten patients had major adverse effects and 1820 patients experienced minor adverse effects. Myocardial infarction occurred in 4 patients, 3 of whom had unstable angina before scanning. Six patients developed acute bronchospasm, 4 of whom had a history of asthma or had wheezing before using dipyridamole. Adverse effects considered to be minor included chest pain in 19.7% of patients, ST-T-segment depression in 7.5%, ventricular extrasystoles in 5.2%, headache in 12.2%, dizziness in 11.8%, nausea in 4.6%, and hypotension in 4.6%. Aminophylline was effective in relieving symptoms of adverse effects in 97% of 454 patients.

Hypersensitivity reactions including anaphylaxis and angioedema have been reported.[2,3]

UK licensed product information contra-indicates intravenous dipyridamole in patients with hypotension, unstable angina, aortic stenosis, recent myocardial infarction, heart failure, coagulation disorders, arrhythmias, conduction disorders, asthma, or a history of bronchospasm. However, a review[4] of pharmacological stress testing suggested that with appropriate patient selection and adequate monitoring, the incidence of life-threatening adverse reactions is negligible. It was also considered that dipyridamole-thallium-201 imaging could be safely performed in the early post-myocardial infarction period.

1. Ranhosky A, *et al.* The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990; **81:** 1205–9.
2. Weinmann P, *et al.* Anaphylaxis-like reaction induced by dipyridamole during myocardial scintigraphy. *Am J Med* 1994; **97:** 488.
3. Angelides S, *et al.* Acute reaction to dipyridamole during myocardial scintigraphy. *N Engl J Med* 1999; **340:** 394.
4. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.

Interactions

Dipyridamole may enhance the actions of oral anticoagulants due to its antiplatelet effect. It inhibits the reuptake of adenosine and may enhance its effects; the dose of adenosine must be reduced if both drugs are given. Dipyridamole may also inhibit the uptake of fludarabine and may reduce its efficacy.

The absorption of dipyridamole may be reduced by drugs such as antacids that increase gastric pH.

Anticoagulants. Dipyridamole may induce bleeding in patients receiving oral anticoagulants without altering prothrombin times (see Antiplatelets, under Warfarin, Interactions, p.1429).

Xanthines. Xanthines may antagonise some of the effects of dipyridamole due to their action as adenosine antagonists. *Aminophylline* may be used to reverse some of the adverse effects of dipyridamole. Intravenous *caffeine* has been reported[1] to attenuate the haemodynamic response to dipyridamole and it has been suggested that caffeine should be avoided for at least 24 hours before the test in patients receiving dipyridamole for myocardial imaging.

1. Smits P, *et al.* Dose-dependent inhibition of the hemodynamic response to dipyridamole by caffeine. *Clin Pharmacol Ther* 1991; **50:** 529–37.

Pharmacokinetics

Dipyridamole is incompletely absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 75 minutes after an oral dose. Dipyridamole is more than 90% bound to plasma proteins. A terminal half-life of 10 to 12 hours has been reported. Dipyridamole is metabolised in the liver and is mainly excreted as glucuronides in the bile. Excretion may be delayed by enterohepatic recirculation. A small amount is excreted in the urine. Dipyridamole is distributed into breast milk.

◊ References.

1. Mahony C, *et al.* Dipyridamole kinetics. *Clin Pharmacol Ther* 1982; **31:** 330–8.
2. Mahony C, *et al.* Plasma dipyridamole concentrations after two different dosage regimens in patients. *J Clin Pharmacol* 1983; **23:** 123–6.

Uses and Administration

Dipyridamole is an adenosine reuptake inhibitor and phosphodiesterase inhibitor with antiplatelet and vasodilating activity and is used in thromboembolic disorders (p.1187). Oral dipyridamole is used for the prophylaxis of thromboembolism after cardiac valve replacement (p.1187) and in the management of stroke (below); it has also been used in the management of myocardial infarction (p.1175). Dipyridamole given intravenously results in marked coronary vasodilatation and is used in stress testing in patients with ischaemic heart disease (see Myocardial Imaging, below).

For the prophylaxis of **thromboembolism** after cardiac valve replacement, dipyridamole is given with an oral anticoagulant. The usual adult dose is 300 to 600 mg daily by mouth in divided doses before meals. Children have been given 5 mg/kg by mouth daily in divided doses.

For the secondary prevention of **stroke** or transient ischaemic attack dipyridamole is given as a modified-release preparation, alone or with aspirin, in a dose of 200 mg twice daily.

◊ General references.

1. FitzGerald GA. Dipyridamole. *N Engl J Med* 1987; **316:** 1247–57.
2. Gibbs CR, Lip GYH. Do we still need dipyridamole? *Br J Clin Pharmacol* 1998; **45:** 323–8.

Myocardial imaging. Perfusion abnormalities due to coronary artery disease are usually absent at rest but are present during stress, and stress imaging may therefore be used in the assessment of myocardial function. The stress is usually supplied by exercise, but when exercise is inappropriate pharmacological methods such as dipyridamole may be used.

Dipyridamole has been used with thallium-201 scintigraphy in adults and children and is usually given intravenously in a dose of 567 micrograms/kg over 4 minutes. Thallium-201 is given within 3 to 5 minutes after completion of the infusion of dipyridamole. Initial images are obtained after 5 minutes and delayed images are obtained 2.5 to 4 hours later. Dipyridamole (300 to 400 mg) has also been given as an oral suspension; thallium-201 is given about 45 minutes later to coincide with peak dipyridamole-serum concentrations.

Dipyridamole has also been used in echocardiography.[1,2] The intravenous dipyridamole dose used to obtain maximum sensitivity is often higher (750 to 840 micrograms/kg) than the dose used in scintigraphy.[1]

1. Beller GA. Pharmacologic stress imaging. *JAMA* 1991; **265:** 633–8.
2. Buchalter MB, *et al.* Dipyridamole echocardiography: the bedside stress test for coronary artery disease. *Postgrad Med J* 1990; **66:** 531–5.

Stroke. The value of long-term antiplatelet therapy with aspirin in patients who have suffered an ischaemic stroke (p.1185) or transient ischaemic attack is well-established, with a reduction in the risk of both stroke and other vascular events.[1] The use of dipyridamole has been more controversial. Early studies with dipyridamole, used alone or with aspirin, failed to show any benefit over aspirin alone. The European Stroke Prevention Study-2 (ESPS-2),[2] which compared aspirin and dipyridamole, alone or together, with placebo, found that both drugs reduced the risk of stroke and that the effects appeared to be additive. The study