
AUSTRALIAN PRODUCT INFORMATION – PERSANTIN® (DIPYRIDAMOLE) INJECTION AMPOULE

1. NAME OF THE MEDICINE

Dipyridamole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PERSANTIN Ampoules contain dipyridamole 10 mg in 2 mL and are intended for intravenous administration. For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

PERSANTIN 10 mg/2 mL solution for injection is a clear, yellow solution practically free from suspended particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

PERSANTIN Ampoules are indicated as an alternative to exercise in myocardial imaging.

4.2 Dose and method of administration

Perfusion imaging: The dose of intravenous PERSANTIN as an adjunct to myocardial perfusion imaging should be adjusted according to the weight of the patient. The recommended dose is 0.14 mg/kg/min (0.56 mg/kg total) infused over 4 minutes. Although the maximum tolerated dose has not been determined, clinical experience suggests that a total dose beyond 60 mg is not needed for any patient.

Stress echo: The recommended protocol for intravenous dosing is 0.56 mg/kg over a 4 minute period, followed by 4 minutes of no dose, and if echo monitoring performed and analysed in real time shows no changes, by an additional 0.28 mg/kg over 2 minutes, yielding a cumulative dosage of 0.84 mg/kg over 10 minutes. This “high dose” protocol may also be given in 6 minutes. Most experience has been gained using a total dose of 0.84 mg/kg over 10 minutes or 6 minutes, therefore it is not recommended to exceed this dose for diagnostic testing.

Prior to intravenous administration, PERSANTIN should be diluted in at least a 1:2 ratio with sodium chloride 0.45% or 0.9% or glucose 5% to a total volume of approximately 20 to 50 mL. Infusion of undiluted PERSANTIN may cause local irritation. The imaging agent should be injected within 5 minutes following administration of intravenous PERSANTIN.

PERSANTIN for intravenous administration should not be mixed with other drugs in the same syringe or infusion container.

4.3 Contraindications

Hypersensitivity to any of the components of the product.

Acute myocardial infarction. Unstable angina. Uncontrolled cardiac arrhythmias causing symptoms or haemodynamic compromise. Symptomatic severe aortic stenosis. Uncontrolled symptomatic heart failure. Acute pulmonary embolus or pulmonary infarction. Acute myocarditis or pericarditis. Active endocarditis. Acute aortic dissection.

Patients already receiving treatment with regular oral dipyridamole should not receive additional intravenous PERSANTIN.

4.4 Special warnings and precautions for use

The potential clinical information to be gained through use of intravenous PERSANTIN as an adjunct in myocardial imaging must be weighed against the risk to the patient. Comparable reactions to exercise-induced stress may occur, and therefore appropriate monitoring is indicated. Patients with a history of severe coronary heart disease may be at a greater risk.

Patients with asthma, baseline hypotension (systolic pressure <90 mm Hg), recent unexplained syncope or transient ischaemic attacks should not be treated with intravenous dipyridamole.

Caution should be taken in patients with left main coronary stenosis, moderate stenotic valvular heart disease, electrolytic abnormalities, severe arterial hypertension (systolic pressure >200 mm Hg and/or diastolic pressure >110 mm Hg), tachyarrhythmias or bradyarrhythmias, hypertrophic cardiomyopathy and other forms of outflow tract obstruction, or high-degree atrioventricular block.

Patients using dipyridamole, theophylline or caffeine chronically should not undergo testing for at least 24 hours after withdrawal of therapy because adenosine blood levels could be unpredictably high. If pharmacological stress testing with intravenous dipyridamole is considered necessary, drugs containing oral dipyridamole (e.g. ASASANTIN SR, PERSANTIN) should be discontinued for twenty-four hours prior to the stress testing. Failure to do so may impair the sensitivity of the test.

In patients with myasthenia gravis, the possibility of an interaction between dipyridamole and cholinesterase inhibitors should be considered (see section 4.5 Interactions with other medicines and other forms of interactions).

Serious adverse reactions associated with the intravenous administration of PERSANTIN for myocardial imaging have been reported (see section 4.8 Adverse effects (Undesirable effects)).

Most of the adverse effects of dipyridamole may be reversed with intravenous aminophylline, but it is not recommended that this be given routinely. If variant angina (elevated ST segments) is induced by dipyridamole, then it may be worsened by aminophylline and alternative vasodilators such as nitrates should be given.

Use in the elderly

No data available.

Paediatric Use'

Safety and efficacy in children have not been established.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interaction

Xanthine derivatives (e.g. caffeine and theophylline) can weaken the vasodilating effect of dipyridamole and should therefore be avoided 24 hours before myocardial imaging with intravenous PERSANTIN.

Dipyridamole increases the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should be considered.

Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs and may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

When dipyridamole is used in combination with anticoagulants or aspirin, the statements on intolerance and risks for these preparations must be observed. Addition of dipyridamole to aspirin does not increase the incidence of bleeding events. When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No studies on the effect on human fertility have been conducted with intravenous PERSANTIN.

Use in pregnancy (Category B1)

Drugs in this category have been taken by only a limited number of pregnant women and women of child-bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

However, the usual precautions regarding the use of medication at this time, especially during the first trimester, should be observed.

Use in lactation

Dipyridamole has been reported to distribute into breast milk. Caution should therefore be used when the drug is administered to nursing mothers.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness during treatment with intravenous PERSANTIN. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Adverse effects (Undesirable effects)

When intravenous PERSANTIN is used as an adjunct to myocardial perfusion imaging, the following adverse effects have been reported:

Immune system disorders: hypersensitivity, anaphylactoid reactions, angioedema

Nervous system disorders: headache, dizziness, paraesthesia, transient ischaemic attacks, cerebrovascular accident, convulsion

Cardiac disorders: chest pain/angina pectoris, arrhythmia, tachycardia, myocardial infarction, bradycardia, cardiac arrest, ventricular fibrillation, syncope, sinus arrest, atrioventricular block

Vascular disorders: hypotension, hot flush

Respiratory, thoracic and mediastinal disorders: bronchospasm, laryngospasm

Gastrointestinal disorders: nausea, abdominal pain, diarrhoea, vomiting

Skin and subcutaneous tissue disorders: urticaria, rash

Musculoskeletal, connective tissue and bone disorders: myalgia

General disorders and administration site conditions: cardiac death, oedema

Investigations: electrocardiogram ST-T change, electrocardiogram change.

There have also been rare reports of cerebral seizure/grand mal seizure. For high doses of intravenous dipyridamole as used in cardiac imaging, more frequent and severe adverse reactions have been reported than those reported during oral administration of dipyridamole at the recommended doses in therapeutic indications. Nevertheless, all available data suggest that the benefit-risk ratio is at least as favourable as the benefit-risk ratio of conventional exercise testing.

When intravenous PERSANTIN was used as an adjunct to myocardial perfusion imaging in a study of 3911 patients, the adverse events occurring at a frequency of 1% or greater in patients are shown in the following table:

Event	Incidence (%), n=3911
Chest pain/angina pectoris	19.7
Headache	12.2
Dizziness	11.8
ST-T changes	7.5
Ventricular extrasystoles	5.2
Hypotension	4.6
Nausea	4.6
Flushing	3.4
Tachycardia	3.2
Dyspnoea	2.6
Pain (unspecified)	2.6
Blood pressure lability	1.6
Hypertension	1.5

Paraesthesia	1.3
Fatigue	1.2
Dyspepsia	1.0

Safety data were obtained from a review of 7 published studies (n=89482) and serious adverse events are reported in the following table:

Event	Number of events (frequency), n=89482
Pulmonary oedema	1
Transient ischaemic attack	9
Bronchospasm	15
Asystole	1
Sustained ventricular tachycardia or ventricular fibrillation	7
Non-fatal myocardial infarction	17 (1.8/10000)
Death	10(1/9000)
Any complication	60

Monitoring of Patients

When myocardial imaging is performed with intravenous PERSANTIN, parenteral aminophylline should be readily available for relieving adverse effects such as bronchospasm or chest pain. Vital signs should be monitored during and for 10-15 minutes following the intravenous infusion of PERSANTIN and an electrocardiographic tracing should be obtained using at least one chest lead. Should severe chest pain or bronchospasm occur, aminophylline may be administered by slow intravenous injection (50-100 mg over 30 to 60 seconds) in doses ranging from 50 to 250 mg. Nitroglycerin (sublingual or intravenous) may be administered if aminophylline fails to completely eliminate ischaemia. If chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered.

In the case of severe hypotension, the patient should be placed in a supine position with the head tilted down if necessary, before administration of parenteral aminophylline.

If 250 mg aminophylline does not relieve chest pain symptoms within a few minutes, sublingual nitroglycerin may be administered.

If the clinical condition of a patient with an adverse effect permits a one minute delay in the administration of parenteral aminophylline, the imaging agent may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial perfusion imaging to be performed before reversal of the pharmacological effects of intravenous PERSANTIN on the coronary circulation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

Symptoms

No cases of overdosage in humans have been reported in this indication. It is unlikely that overdosage will occur because of the nature of use (i.e. single intravenous administration in controlled settings).

Signs and symptoms as described under section 4.8 Adverse effects (Undesirable effects) would be expected to occur. These could be severe in certain individuals.

Treatment

Symptomatic therapy is recommended.

Should severe chest pain or bronchospasm occur, parenteral aminophylline may be administered by slow intravenous injection (50-100 mg over 30 to 60 seconds) in doses ranging from 50 to 250 mg. Nitroglycerin (sublingual or intravenous) may be administered if aminophylline fails to completely eliminate ischaemia.

Due to its wide distribution to tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Dipyridamole is a coronary vasodilator. It produces vasodilation indirectly via two mechanisms, namely the inhibition of adenosine uptake which leads to an increase in the circulating adenosine, and the inhibition of cGMP-phosphodiesterase.

Vasodilation induced by intravenous PERSANTIN leads to regional redistribution of coronary blood flow and may lead to abnormalities in the distribution of imaging agent and ventricular function in patients with coronary artery disease. The normal vessels dilate with enhanced flow, leaving relatively reduced pressure and flow across areas of haemodynamically important coronary stenoses.

Dipyridamole also has an antithrombotic action.

Clinical Trials

In a review of published literature dipyridamole perfusion imaging was examined in 32 studies. With the exception of one study, dipyridamole perfusion imaging was compared with coronary arteriography. A single study compared exercise and dipyridamole in patients undergoing thallium-201 myocardial imaging. A total of 2240 patients were assessed in these studies. Information on the total number of patients with coronary artery disease was not available. With the exception of one study where sensitivity was only 37%, sensitivity ranged from 67% to 100%. There was one study with a specificity of 28%, specificity in remaining studies ranged from 50% to 96%. Pooling these studies gave a combined sensitivity of 86% and specificity of 74%.

Dipyridamole stress echocardiography was compared with coronary arteriography in 28 studies. A total of 2137 patients were assessed with 1296 (61%) diagnosed as having coronary artery disease. Sensitivity of dipyridamole stress echocardiography ranged from 32% to 100% and specificity from 72% to 100%. The combined results from these studies gave a sensitivity of 73% and specificity of 91%.

The prognosis following dipyridamole stress testing was examined in 59 studies where patients had undergone dipyridamole perfusion imaging. All but 3 studies confirmed that an abnormal dipyridamole stress study was associated with more subsequent cardiac events than a normal study. Prognosis following dipyridamole stress echocardiography was examined in 21 studies. An abnormal test was predictive of more subsequent cardiac events than a normal study. Typically, with either technique in a group of patients with intermediate risk of coronary artery disease, an abnormal study suggested a cardiac event post-operatively in 20% and a normal study in only 2%.

5.2 Pharmacokinetic properties

(Most pharmacokinetic data refer to healthy volunteers.)

Adequate curve fitting is achieved by a 3 compartment model:

- (a) A rapid alpha phase, with a half-life of about 3 minutes, presumably reflecting distribution of the drug from the central compartment to peripheral compartments;
- (b) A beta phase, with a half-life of about 40 minutes, which represents the elimination of most of the administered drug and, together with the alpha phase, accounts for about 70% of the total area under the plasma concentration time curve (AUC);
- (c) A final, prolonged terminal elimination phase (gamma) with a half-life of about 15 hours. This represents about 30% of the total AUC and probably represents the rediffusion of a smaller proportion of the administered dose from remotely accessible tissues of low capacity back into the central compartment. This may also reflect some enterohepatic recycling (which is evident from smaller secondary peaks several hours after the end of the infusion at time points which are related to food intake).

At the end of a 4 minute infusion of 0.5 mg/kg, mean dipyridamole plasma concentration was 6.30 ± 0.32 $\mu\text{g/mL}$, while at 1 hour afterwards the mean plasma concentration was 1.13 ± 0.36 $\mu\text{g/mL}$.

Distribution

On account of its high lipophilicity, log P 3.92 (n-octanol/0.1N NaOH), dipyridamole distributes to many organs. In animals, dipyridamole is distributed preferentially to the liver, then to the lungs, kidneys, spleen and heart. Dipyridamole does not cross the blood-brain barrier.

The apparent volume of distribution of the central compartment (V_c) is about 5 L (similar to plasma volume). The apparent volume of distribution at steady state is about 100-140 litres, reflecting distribution to various compartments. Total clearance is approximately 200 mL/min and mean residence time is about 7 hours.

Placental transfer of dipyridamole is very low. It is known to be excreted into breast milk.

Protein binding of dipyridamole is about 97-99%. It is primarily bound to alpha 1-acid glycoprotein and albumin.

Metabolism and excretion

Dipyridamole is metabolised in the liver predominantly to form a monoglucuronide and only small amounts of diglucuronide, desalkyl dipyridamole and a hydroxy compound. After intravenous treatment, the amount of glucuronides is about 10%. Renal excretion is about 5%.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients are: tartaric acid, macrogol 600, hydrochloric acid (to adjust pH) and water for injections.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PERSANTIN Ampoules 10 mg/2 mL are supplied in glass ampoules.

Boxes of 5 ampoules.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Dipyridamole is an odourless, yellow crystalline powder with a bitter taste. It has a melting point in the range of 164-168°C, and is soluble in dilute acids, methanol, ethanol and chloroform.

Chemical structure

Approved Name: Dipyridamole

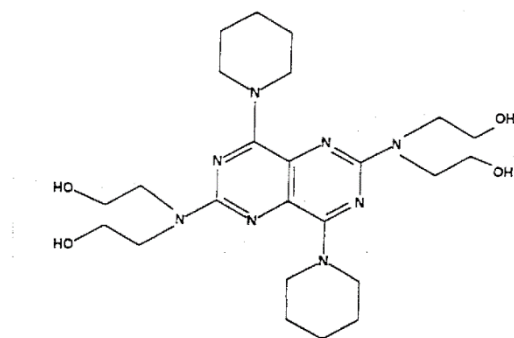
Chemical Name: 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido[5,4-d]pyrimidine

Laboratory Code: R-A 8-BS

Molecular Formula: $C_{24}H_{40}N_8O_4$

Molecular Weight: 504.6

Structural Formula:



CAS number

58-32-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Clinect Pty Ltd

120-132 Atlantic Drive

Keysborough, VIC 3173

Australia

Free call Australia: 1800 899 005

9. DATE OF FIRST APPROVAL

29 August 2000

10. DATE OF REVISION

27 January 2021

Summary Table of Changes

Section Changed	Summary of New Information
1, 4.8	Editorial
8	Sponsor Change