Persantin®

Boehringer Ingelheim

Composition

Yellow, clear solution.

1 ampoule of 2 ml contains	10 mg
1 vial of 10 ml contains	50 mg

2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido(5,4-d)-pyrimidine (= dipyridamole)

Properties

Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells in vitro and in vivo; the inhibition amounts to 80% at its maximum and occurs dose-dependently at concentrations of 0.5 - 2 mcg/ml. Consequently, there is an increased concentration of adenosine locally to act on the platelet A2-receptor, stimulating platelet adenylate cyclase, thereby increasing platelet cAMP levels. Thus, platelet aggregation in response to various stimuli such as PAF, collagen and ADP is inhibited. Reduced platelet aggregation reduces platelet consumption towards normal levels. In addition, adenosine has a vasodilator effect and this is one of the mechanisms by which dipyridamole produces vasodilation.

Presumably via a 'steal effect' the vasodilation induced by PERSANTIN administered i.v. in doses used for cardiac imaging techniques leads to regional redistribution of coronary blood flow and may lead to abnormalities in thallium distribution 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 inhibits phosphodiesterase (PDE) in various tissues. Whilst the inhibition of cAMP-PDE is weak, therapeutic levels inhibit cGMP-PDE, thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, identified as NO).

Dipyridamole also stimulates the biosynthesis and release of prostacyclin by the endothelium.
Dipyridamole reduces the thrombogenicity of subendothelial structures by increasing the concentration of the protective mediator 13-HODE (13-hydroxyoctadecadienic acid).

Pharmacokinetics

(Most pharmacokinetic data refer to healthy volunteers.)
Adequate curve fitting with i.v. administration (60 mg/75 min) is achieved by a 3 compartment model:

a) A rapid alpha phase, with a half-life of about 3 min, presumably reflecting distribution of the drug from the central compartment to peripheral compartments;
b) A beta phase, with a half-life of about 40 min, which represents the elimination of most of the administered drug and accounts for about 70% (together with the alpha phase) of the total AUC; i.e. dominant half-life
c) A final, prolonged terminal elimination phase ($gamma_Z$) with a half-life of about 13 hours. This represents about 30% of the total area under the plasma concentration time curve 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 end of the infusion at time points which are related with food intake).

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 l, reflecting distribution to various compartments. Total clearance is approximately 200 ml/min and mean residence time is 6.4 hours.

Distribution of dipyridamole

Owing to 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.
The drug does not cross the blood-brain barrier to a significant extent.
Placental transfer of dipyridamole is very low. Non-clinical data have also shown that dipyridamole can be excreted in breast milk
Protein binding of dipyridamole is about 97 - 99%, primarily it is bound to alpha 1-acid glycoprotein and albumin.

Metabolism of dipyridamole

Metabolism of dipyridamole occurs in the liver. Dipyridamole is metabolized by conjugation with glucuronic acid to form mainly a monoglucuronide and only small amounts of diglucuronide.
After i.v. treatment, glucuronide concentrations are approx. 10% of total drug.

Elimination of dipyridamole

Renal excretion of parent compound is negligible (< 0.5%). Urinary excretion of the glucuronide metabolite is low (< 8%), the metabolites are mostly (about 95%) excreted via the bile into the faeces, with some evidence of entero-hepatic recirculation.

Kinetics in elderly subjects

Plasma concentrations (determined as AUC) in elderly subjects (> 65 years) were about 30 - 50% higher with oral treatment than in young (< 55 years) subjects and the difference is caused mainly by reduced clearance; a slower decrease of plasma concentrations after i.v. treatment is to be expected.

Kinetics in patients with hepatic impairment

Patients with hepatic insufficiency show no change in plasma concentrations of dipyridamole, but an increase of (pharmacodynamically low active) glucuronides. It is suggested to dose dipyridamole without restriction as long as there is no clinical evidence of liver failure.

Kinetics in patients with renal impairment

Since renal excretion is very low (5 %), no change in pharmacokinetics is to be expected in cases of renal insufficiency. In the ESPS2 trial, in patients with creatinine clearances ranging from about 15 ml/min to >100 ml/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

Indications

I.v. PERSANTIN is indicated as an alternative to exercise testing in myocardial perfusion Thallium and stress-echocardiography imaging for the evaluation of coronary artery disease, particularly in patients who cannot exercise adequately. The sensitivity and specificity of exercise thallium imaging and PERSANTIN thallium imaging is almost identical.

Dosage and Administration

The dose of intravenous PERSANTIN as an adjunct to thallium myocardial perfusion imaging should be adjusted according to the weight of the patient. The recommended dose is 0.142 mg/kg/minute (0.567 mg/kg total) infused over 4 minutes. The maximum dose is 0.84 mg/kg infused over 6 - 10 minutes. Exceeding the maximum dose is not recommended.
Prior to intravenous administration, i.v. PERSANTIN should be diluted in at least a 1:2 ratio with sodium chloride 0.45% or 0.9% or glucose 5% for a total volume of approximately 20 to 50 ml. Infusion of undiluted PERSANTIN may cause local irritation. Thallium-201 should be injected within 5 minutes following the 4-minute infusion of PERSANTIN.
PERSANTIN should not be mixed with other drugs in the same syringe or infusion container.
Safety and effectiveness in children have not been established. Use is not recommended.

Contraindications
Hypersensitivity to any of the components of the product.
Patients already receiving treatment with regular oral PERSANTIN should not receive additional intravenous PERSANTIN for the purposes of stress testing.

Special Warnings and Precautions
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, together with patients with a history of asthma.

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, 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.

Clinical experience suggests that patients being treated with oral dipyridamole who also require pharmacological stress testing with intravenous dipyridamole, should discontinue drugs containing oral dipyridamole for twenty-four hours prior to stress testing. Failure to do so may impair the sensitivity of the test.

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 chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered.

If the clinical condition of a patient with an adverse effect permits a one minute delay in the administration of parenteral aminophylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial thallium perfusion imaging to be performed before reversal of the pharmacologic effects of PERSANTIN on the coronary circulation.

In patients with myasthenia gravis, the possibility of an interaction between dipyridamole and cholinesterase inhibitors should be considered (see: Interaction).

Side Effects
When using PERSANTIN as an adjunct to myocardial imaging, the following adverse events have been reported:

<u>Immune system disorders</u>
hypersensitivity
anaphylactoid reaction
angioedema

<u>Nervous system disorders</u>
headache
dizziness
paresthesia
transient ischaemic attack
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

At high doses of intravenous dipyridamole as used in cardiac imaging, more frequent and severe side effects have been reported than those reported during either intravenous or oral administration of dipyridamole at the recommended doses. Nevertheless, all available data suggest that the benefit-risk ratio is at least as favourable as the benefit-risk ratio of conventional exercise testing.

Drug Interactions
Xanthine derivatives (e.g caffeine and theophylline) can potentially reduce the vasodilating effect of dipyridamole and should therefore be avoided 24 hours before myocardial imaging with PERSANTIN.
Dipyridamole increases plasma levels and cardiovascular effects of adenosine.
Dipyridamole may increase the hypotensive effect of drugs which reduce blood pressure and may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

In patients already receiving oral dipyridamole clinical experience suggests that the sensitivity of the intravenous dipyridamole stress test may be impaired.
Oral dipyridamole treatment should be discontinued for twenty-four hours prior to testing.

Fertility, Pregnancy and Lactation

Pregnancy
There is inadequate evidence of safety in human pregnancy, but PERSANTIN has been used for many years without apparent ill-consequence. Preclinical studies have shown no hazard.
Nevertheless, medicines should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh the possible risk to the foetus.

Lactation
PERSANTIN should only be used during lactation if considered essential by the physician.

Fertility
No studies on the effect on human fertility have been conducted with i.v. PERSANTIN. Non-clinical studies with dipyridamole did not indicate direct or indirect harmful effects with respect to the fertility index.

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 i.v. 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.

Overdosage

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 Side Effects are expected to occur and could be even more severe in single cases.

Therapy
Symptomatic therapy is recommended.
Should severe chest pain or brochospasm 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.
Due to its wide distribution to tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

Availability
Ampoules of 10mg/2ml

Pack sizes
Box of 5 ampoule

Store below 25^{o}C
Please refer to the packaging for information on shelf-life

Manufactured by
Boehringer Ingelheim Espana SA

For
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

Store in a safe place out of the reach of children!