NAME OF THE MEDICINE

Approved Name: Dipyridamole
Chemical Name: 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido[5,4-d]-pyrimidine
CAS No: 58-32-2
Laboratory Code: R-A 8-BS
Molecular Formula: C_{24}H_{40}N_{8}O_{4}
Molecular Weight: 504.6
Structural Formula:

![Structural Formula Image]

DESCRIPTION

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.

PERSANTIN Tablets are available in two strengths containing dipyridamole 25mg or 100mg.

The inactive ingredients in PERSANTIN 25mg Tablets are: lactose, starch-maize (dried), starch-maize (soluble), silica-colloidal anhydrous, magnesium stearate, sucrose, talc-purified, acacia, titanium dioxide, macrogol 6000, beeswax-white, carnauba wax, sunset yellow FCF (Cl 15985).

The inactive ingredients in PERSANTIN 100mg Tablets are: calcium hydrogen phosphate anhydrous, starch-maize (dried), starch-maize (soluble), silica-colloidal anhydrous, sunset yellow FCF (Cl 15985), magnesium stearate, sucrose, talc-purified, acacia, titanium dioxide, macrogol 6000, beeswax-white, carnauba wax.
PHARMACOLOGY

PERSANTIN has an antithrombotic action based on its ability to modify various aspects of platelet function. It causes inhibition of platelet adhesion and aggregation, particularly in diseased states where platelet stickiness is above normal, and lengthens abnormally shortened platelet survival time. These actions are useful in limiting the initiation of thrombus formation.

The mechanism of antiplatelet action is believed to be related to inhibition of the uptake of adenosine by red blood cells and platelets; weak inhibition of cAMP phosphodiesterase which potentiates the aggregation-inhibiting effects of adenosine on platelets; and inhibition of cGMP phosphodiesterase which potentiates the anti-aggregating effects of EDRF (endothelium derived relaxing factor).

PERSANTIN is also a coronary vasodilator.

Pharmacokinetics

Absorption and plasma concentrations

Dipyridamole is rapidly absorbed following oral administration with peak plasma concentrations occurring within 45-75 minutes. Plasma concentrations are quite variable in healthy volunteers and steady state conditions are generally reached within 2 days. There is no cumulation with repetitive dosing. The decline in plasma concentration after oral administration fits a two compartment model. The alpha half life (the initial decline following peak plasma concentration), which represents elimination of the majority of administered drug, has been reported to be about 30-60 minutes and the beta half life (the terminal decline in plasma concentration) approximately 10-12 hours. Total plasma clearance has been reported to be 8.27 L/hr. Dipyridamole may undergo entero-hepatic recirculation.

The absolute bioavailability is limited by first pass hepatic metabolism and incomplete oral absorption and is reported to range from 40-70%.

Distribution

Animal studies have shown that dipyridamole is widely distributed, preferentially to the liver, lungs, kidney, spleen and heart. In man the apparent volume of distribution is about 140 litres, and 97-99% of the drug is bound to plasma protein. Dipyridamole does not cross the blood brain barrier.

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

Metabolism

Dipyridamole is metabolised in the liver.

Excretion

It is mainly excreted as glucuronides in the bile. A small amount (1-5%) is excreted in the urine.

INDICATIONS

PERSANTIN Tablets are indicated in combination with anticoagulants for the prevention of post-operative thromboembolic complications associated with prosthetic heart valves.
CONTRAINDICATIONS

Hypersensitivity to any of the components of the product.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see PRECAUTIONS) the use of the product is contraindicated.

PRECAUTIONS

Because PERSANTIN is a potent vasodilator, high doses should be used with caution in patients with severe coronary artery disease (e.g. unstable angina or recently sustained myocardial infarction), subvalvular aortic stenosis or haemodynamic instability (e.g. decompensated heart failure).

Patients treated with regular oral doses of PERSANTIN tablets should not receive additional intravenous dipyridamole. 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.

During treatment with PERSANTIN, readjustment of therapy may be necessary in patients with myasthenia gravis (see INTERACTIONS WITH OTHER MEDICINES).

A small number of cases have been reported in which unconjugated dipyridamole was shown to be incorporated into gallstones to a variable extent (up to 70% by dry weight of stone). These patients were all elderly, and had evidence of ascending cholangitis, and had been treated with oral dipyridamole for a number of years. There is no evidence that dipyridamole was the initiating factor in causing gallstones to form in these patients. It is possible that bacterial deglucuronidation of unconjugated dipyridamole in bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

PERSANTIN 25mg Tablets: One sugar-coated tablet contains 13 mg sucrose and 25 mg lactose monohydrate, resulting in 312 mg sucrose and 600 mg lactose monohydrate per maximum recommended daily dose for adults. Patients with the rare hereditary conditions of fructose intolerance or galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PERSANTIN® 25 mg Tablets contain the excipient sunset yellow (E 110), which may cause allergic reactions.

PERSANTIN 100mg Tablets: One sugar-coated tablet contains 49 mg sucrose, resulting in 294 mg sucrose per maximum recommended daily dose for adults. Patients with the rare hereditary conditions of fructose intolerance should not take this medicine.

Effects on fertility

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

Use in Pregnancy (Category B1)

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.

**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 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.

**INTERACTIONS WITH OTHER MEDICINES**

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

When dipyridamole is used in combination with any substances impacting coagulation such as anticoagulants and antiplatelets, the safety profile for these medications must be observed.

Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs.

Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

**ADVERSE EFFECTS**

Adverse effects at therapeutic doses are usually mild and transient.

*Blood and lymphatic system disorders*: thrombocytopenia

*Immune system disorders*: hypersensitivity, angioedema

*Nervous system disorders*: headache, dizziness

*Cardiac disorders*: angina pectoris, tachycardia

*Vascular disorders*: hypotension, hot flush

*Respiratory, thoracic and mediastinal disorders*: bronchospasm

*Gastrointestinal disorders*: diarrhoea, nausea, vomiting

*Skin and subcutaneous tissue disorders*: rash, urticaria

*Musculoskeletal, connective tissue and bone disorders*: myalgia
Injury, poisoning and procedural complications: post procedural haemorrhage, operative haemorrhage

Dipyridamole has been shown to be incorporated into gallstones (see PRECAUTIONS).

**DOSAGE AND ADMINISTRATION**

Usually 100mg four times a day, taken approximately one hour before meals.

**OVERDOSAGE**

**Symptoms**

Symptoms such as feeling warm, flushes, sweating, accelerated pulse, restlessness, feeling of weakness and dizziness, drop in blood pressure and anginal complaints may occur.

**Treatment**

General supportive measures.

Since the vasodilating action of PERSANTIN is counteracted by xanthine derivatives, slow i.v. administration of aminophylline (50-100 mg over 30 to 60 seconds) may be helpful. If 250 mg aminophylline does not relieve anginal complaints, sublingual nitroglycerin may be administered.

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

**PRESENTATION AND STORAGE CONDITIONS**

PERSANTIN 100mg Tablets: White, round, sugar-coated tablets each containing Dipyridamole 100mg. Cartons of 100 tablets.

PERSANTIN 25mg Tablets: Orange, round, sugar-coated tablets each containing Dipyridamole 25mg. Bottles of 100 tablets.

Storage: Store below 30°C.

Not all pack sizes and presentations are being distributed in Australia.

**NAME AND ADDRESS OF THE SPONSOR**

BOEHRINGER INGELHEIM PTY LIMITED
ABN 52 000 452 308
78 WATERLOO ROAD
NORTH RYDE NSW 2113

**POISON SCHEDULE OF THE MEDICINE**

S4 – Prescription Only Medicine
Approved by the Therapeutic Goods Administration (TGA): 24 September 1996.

Date of most recent amendment: 9 September 2011.