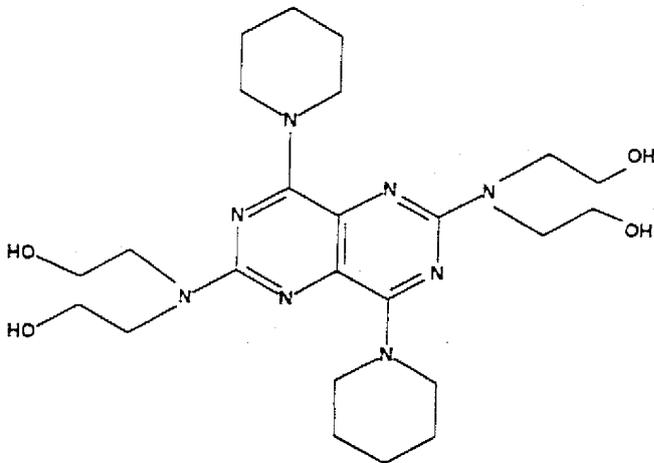


PERSANTIN[®] SR

(Dipyridamole)

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: C₂₄H₄₀N₈O₄
Molecular Weight: 504.6
Structural Formula:



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.

The inactive ingredients in PERSANTIN[®] SR 200 mg sustained-release capsules are: tartaric acid, povidone, methacrylic acid copolymer (Eudragit S 100), talc, acacia, hypromellose, hypromellose phthalate, glycerol triacetate, dimethicone 350, stearic acid, gelatin, titanium dioxide, iron oxide red CI77491 and iron oxide yellow CI77492.

PHARMACOLOGY

PERSANTIN[®] SR 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[®] SR is also a coronary vasodilator.

Pharmacokinetics

Absorption and plasma concentrations

Plasma concentrations of dipyridamole from the PERSANTIN[®] SR formulation rise after a lag time of about 30 minutes. Peak plasma levels occur about 2-3 hours after administration, and then decline slowly. Plasma concentrations are quite variable in healthy volunteers and steady state conditions are generally reached within 3 days. Peak concentrations at steady state conditions with a daily dose of 400 mg are about 1.9 (1.2-3.4) µg/mL. 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) is approximately 10-12 hours. Total plasma clearance is about 12 L/hr. Dipyridamole may undergo entero-hepatic recirculation.

The absolute bioavailability of PERSANTIN[®] SR is limited by first pass hepatic metabolism and is about 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 and excretion

Dipyridamole is metabolised in the liver predominantly to form a monoglucuronide which is excreted in the bile. In plasma about 70-80% of the total amount is present as parent compound and 20-30% as the monoglucuronide. Renal excretion is about 5%.

CLINICAL TRIALS

The second European Stroke Prevention Study (ESPS2) was conducted to investigate the effect of sustained-release dipyridamole 200 mg (PERSANTIN[®] SR) twice daily and low-dose aspirin 25 mg twice daily, alone or in combination, for the indications prevention of secondary stroke and transient ischaemic attacks (TIAs). This was a multicentre, multinational, randomised, double-blind, placebo-controlled trial in patients (n=6602) who had experienced a recent ischaemic stroke or TIA. There were 4 parallel treatment groups organised in a 2x2 factorial design with each treatment given for 2 years. Treatments were: placebo; aspirin 25 mg twice daily; PERSANTIN[®] SR (dipyridamole 200 mg) twice daily; and PERSANTIN[®] SR (dipyridamole 200 mg) with aspirin 25 mg (ASASANTIN[®] SR) twice daily. The mean age of the patients was 66.7 years. The qualifying event was TIA in 23.7% of patients and stroke in 73.6% of patients.

The three primary endpoints were: stroke (fatal or not); death from any cause; and stroke and/or death occurring within 2 years of inclusion in the study. Secondary endpoints were myocardial infarction, ischaemic events, other vascular events, vascular deaths, vascular events and TIA. Endpoint data were analysed by calculating for each endpoint the “survival” curves of the four treatment groups. The Cox model was used to identify covariates with significant negative or positive impact upon “survival”.

In terms of stroke prevention, the results showed highly significant differences between the four survival curves ($p < 0.001$). Factorial analysis showed that both drugs were effective ($p < 0.001$), without interaction of one treatment upon the other, and that both given together were additive. Pairwise comparisons demonstrated that the combined therapy with dipyridamole and aspirin resulted in more effective stroke prevention (risk reduction = 37%, $p < 0.001$) than treatment with either aspirin alone (risk reduction = 18%, $p < 0.01$) or dipyridamole alone (risk reduction = 16%, $p < 0.01$). Subgroup analysis based upon demographic criteria, the type of qualifying event or associated risk factors, corroborated the significant treatment effects observed in the total trial population. Subjects who already had a history of cerebrovascular accidents before the qualifying event, had a greater risk reduction of further stroke with combined therapy (48% [$p < 0.001$ compared to placebo]) than subjects in which the qualifying event was the first cerebrovascular accident (29% [$p < 0.01$ compared to placebo]). Subgroup analysis also showed that aspirin and/or dipyridamole were only effective in preventing non-fatal stroke, in contrast to fatal stroke which was not influenced by the treatment. Cox analysis of the “survival” data identified history of a previous cerebrovascular accident before the qualifying event as the most important risk factor predisposing to stroke recurrence, followed by daily alcohol consumption of >5 units/day, diabetes and atrial fibrillation. The same analysis showed that receiving dipyridamole or receiving aspirin were strongly protecting against stroke.

Neither aspirin nor dipyridamole influenced mortality significantly. Effects of dipyridamole and/or aspirin on protection from endpoint stroke and/or death were similar to the effects on stroke. In addition to the prevention of stroke, dipyridamole and/or aspirin were effective in preventing subsequent TIAs, especially in the subgroup of patients in whom TIA was the qualifying event. As was observed for stroke, the efficacy of aspirin and dipyridamole when co-prescribed was additive, being double that of either drug alone. Other relevant events from which occurrence was modified by treatment included ischaemic events, vascular events, and other vascular events (mostly deep venous thrombosis or peripheral arterial occlusion).

The ESPS2 trial shows the efficacy of both sustained-release dipyridamole and low-dose aspirin in preventing stroke. Stroke prevention is even more effective when aspirin and dipyridamole are combined, the benefit being additive. The study also shows that such therapy can prevent recurrence of TIA in patients with a previous history of TIA or stroke.

INDICATIONS

PERSANTIN[®] SR 200 mg sustained-release capsules are indicated for the secondary prevention of ischaemic stroke and transient ischaemic attacks in conjunction with low-dose aspirin. PERSANTIN[®] SR can be used alone if aspirin is not tolerated.

CONTRAINDICATIONS

Hypersensitivity to any of the components of the product.

PRECAUTIONS

Because PERSANTIN[®] SR is a potent vasodilator, it 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[®] SR 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[®] SR readjustment of therapy may be necessary in patients with myasthenia gravis (see INTERACTIONS WITH OTHERMEDICINES).

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.

In the ESPS2 study, PERSANTIN[®] SR was studied in conjunction with aspirin 25 mg twice daily (see CLINICAL TRIALS). The use of PERSANTIN[®] SR with higher doses of aspirin has not been studied, however higher doses of aspirin in combination with dipyridamole have been used in other studies (eg. ESPS1).

Effects on fertility

No studies on the effect on human fertility have been conducted with PERSANTIN[®] SR.

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.

Paediatric use

PERSANTIN[®] SR is not recommended for children.

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® SR. 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 considered.

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

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.

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).

There have been isolated cases of gastroduodenal ulcer and anaemia reported in the clinical study.

Clinical Trial Data

The table below shows adverse events reported in the pivotal clinical trial (ESPS2).

	Number (%) of patients				P*
	Placebo (n=1649)	Aspirin (n=1649)	PERSANTIN® SR (n=1654)	PERSANTIN® SR with Aspirin [†] (n=1650)	
Headache	534 (32.4%)	546 (33.1%)	615 (37.2%)	630 (38.2%)	< 0.001
Dizziness	509 (30.9%)	481 (29.2%)	498 (30.1%)	486 (29.5%)	NS
Dyspepsia	266 (16.1%)	283 (17.2%)	274 (16.6%)	290 (17.6%)	NS
Vomiting	109 (6.6%)	93 (5.6%)	119 (7.2%)	133 (8.1%)	NS
Nausea	226 (13.7%)	204 (12.4%)	245 (14.8%)	254 (15.4%)	NS
Diarrhoea	154 (9.3%)	109 (6.6%)	254 (15.4%)	199 (12.1%)	< 0.01
Gastric pain	219 (13.3%)	242 (14.7%)	240 (14.5%)	274 (16.6%)	NS
Bleeding ^a	74 (4.5%)	135 (8.2%)	77 (4.7%)	144 (8.7%)	< 0.01

* p value (Chi-squared) differences for group homogeneity.

^a Bleeding from any site.

[†] Fixed dose combination containing dipyridamole 200 mg and aspirin 25 mg (ASASANTIN® SR).

NS = no significant differences between treatment groups.

DOSAGE AND ADMINISTRATION

The recommended dose is one capsule twice daily, usually one in the morning and one in the evening, preferably with food.

The capsules should be swallowed whole without chewing.

OVERDOSAGE

Symptoms

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

Treatment

General supportive measures. Since the vasodilating action of PERSANTIN® SR 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

Each PERSANTIN® SR 200 mg sustained-release capsule contains dipyridamole 200 mg. The gelatin shell of the capsule consists of a red opaque cap and an orange opaque body.

Capsules are packed in white polypropylene bottles with child-resistant closures filled with desiccant. Packs contain 10, 20, 30, 50, 60 or 100 capsules.

Storage: Store below 30°C. Protect from moisture.

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

NAME AND ADDRESS OF THE SPONSOR

BOEHRINGER INGELHEIM PTY LIMITED
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78 WATERLOO ROAD
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

Approved by the Therapeutic Goods Administration: 19 November 1998.

Date of most recent amendment: 8 August 2012