PRODUCT MONOGRAPH

Pr PERSANTINE®

Dipyridamole Tablets
Dipyridamole for Injection

50 mg and 75 mg tablets
5 mg/mL injectable ampoules

Coronary Vasodilator
Inhibitor of Platelet Adhesion and Aggregation

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Date of Preparation:
March 15, 1995
Date of Revision:
May 20, 2005

Submission Control No: 092334
BI BPI number: 0248-02 (tablets), 0150-04 (ampoules)

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PERSANTINE®

Dipyridamole Tablets
Dipyridamole for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 50 mg , 75 mg	Acacia, calcium hydrogen phosphate, carnauba wax, colloidal silica, FDC yellow , magnesium stearate, polyethylene glycol, starch, sucrose, talc, titanium dioxide, white wax, and red iron oxide (50 mg tablet only).
i.v (intravenous)	10 mL ampoules, 5 mg/mL	Tartaric acid, polyethylene glycol, hydrochloric acid and sterile water for injection.

INDICATIONS AND CLINICAL USE

Thromboembolic Disease
Persantine (dipyridamole) tablets are indicated for:

- The prevention of post-operative thromboembolic complications associated with prosthetic heart valve.

Myocardial Perfusion Imaging
Persantine (dipyridamole) ampoules can be used to:

- induce pharmacologic vasodilation for myocardial perfusion imaging.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Intravenous administration of Persantine is not recommended in states of shock or collapse.

WARNINGS AND PRECAUTIONS

General

Rare serious adverse reactions associated with the administration of intravenous Persantine for myocardial imaging have been reported. These have included fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, stroke and transient cerebral ischemia.

Cardiovascular

Since excessive doses of dipyridamole (intravenous or oral) or intravenous doses given too rapidly can produce peripheral vasodilation, Persantine should be used with caution in patients with hypotension, coronary artery disease, including rapidly worsening angina, left ventricular outflow obstruction, (including subvalvular aortic stenosis), or hemodynamic instability. In rare cases, such patients may be at risk for developing myocardial ischemia and infarction.

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.

An intravenous bolus of Persantine (40-50 mg over 4 minutes) can result in chest pain in patients with coronary artery disease. Rarely, hypotension or ventricular arrhythmias occur with a rapid, i.v. bolus. The infusion rate should be monitored to minimize this risk. The symptoms can generally be reversed with an intravenous injection of 50-250 mg of aminophylline over several minutes.

Intravenous Persantine (dipyridamole) as an adjunct to myocardial perfusion imaging should be used with caution in patients with unstable angina; as such patients may be at risk for severe myocardial infarction.

As with exercise induced stress, the use of intravenous Persantine as an adjunct to myocardial perfusion imaging may occasionally precipitate cardiac arrhythmias in patients with severe heart disease. Scanning should therefore be performed with constant monitoring of the patient's ECG. Parenteral aminophylline should be readily available and should be administered as a slow intravenous injection of 50-250 mg in the event of occurrences such as chest pain, bronchospasm, severe nausea/vomiting, hypotension, severe headache.

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 of 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 event 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 Persantine on the coronary circulation.

Hepatic/Biliary/Pancreatic

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, 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 conjugated dipyridamole in bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

Respiratory

Patients with a history or presence of bronchial hyperreactivity may be at risk of developing bronchospasm during the use of intravenous Persantine as an adjunct to myocardial perfusion imaging. Although the actual overall incidence of this occurrence is small (~ 0.2%), the clinical information to be gained through the use of intravenous Persantine should be weighed against the potential risk to the patient.

Special Populations

Pregnant Women: Reproductive studies have been performed in mice, rats, and rabbits at doses of up to 125 mg/kg and have not revealed evidence of impaired embryonic development attributable to dipyridamole. However, there have not been adequate, well controlled studies in pregnant women and the drug should be used during pregnancy only if the expected benefits outweigh the potential risks.

Nursing Women: Dipyridamole is excreted in human milk. Caution should therefore be used when this drug is administered to nursing mothers.

Pediatrics: The safety and effectiveness of Persantine have not been established in the pediatric population.

ADVERSE REACTIONS

PARENTERAL ADMINISTRATION (i.v. infusion)

Adverse Drug Reaction Overview

Serious adverse events (fatal and non-fatal myocardial infarction, severe ventricular arrhythmias, and serious CNS abnormalities) associated with the intravenous administration of Persantine for myocardial imaging are described in WARNINGS.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

When intravenous Persantine was used as an adjunct to myocardial perfusion imaging in a study of 3911 patients, the following events occurred in greater than 1% of the patients:

Event Description	Incidence (%) of Occurrence in 3911 Patients
Chest pain/angina pectoris	19.7
Headache	12.2
Dizziness	11.8
Electrocardiographic Abnormalities/ST-T changes	7.5
Electrocardiographic Abnormalities/Extrasystoles	5.2
Hypotension	4.6
Nausea	4.6
Flushing	3.4
Electrocardiographic Abnormalities/Tachycardia	3.2
Dyspnea	2.6
Pain Unspecified	2.6
Blood Pressure Lability	1.6
Hypertension	1.5
Paresthesia	1.3
Fatigue	1.2

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Cardiovascular: Electrocardiographic abnormalities unspecified, arrhythmia unspecified, palpitation, ventricular tachycardia, bradycardia, myocardial infarction, AV block, syncope, orthostatic hypotension, atrial fibrillation, supraventricular tachycardia, ventricular arrhythmia unspecified, heart block unspecified, cardiomyopathy, and edema
Central and Peripheral Nervous System: Hypoaesthesia, hypertonia, nervousness/anxiety, tremor, abnormal coordination, somnolence, dysphonia, migraine, vertigo.
Respiratory: Pharyngitis, bronchospasm, hyperventilation, rhinitis, coughing, pleural pain.
Gastrointestinal: Dyspepsia, dry mouth, abdominal pain, flatulence, vomiting, eructation, dysphagia, tenesmus, increased appetite.
Other: Myalgia, back pain, injection site reaction unspecified, diaphoresis, asthenia, malaise, arthralgia, injection site pain, rigor, earache, tinnitus, vision abnormalities unspecified, dysgeusia, thirst, depersonalization, eye pain, renal pain, perineal pain, breast pain, intermittent

claudication, leg cramping.

Post-Market Adverse Drug Reactions

When using Persantine as an adjunct to myocardial imaging, the following adverse events have been reported: cardiac death, cardiac arrest, myocardial infraction (rarely fatal), arrhythmias (e.g. sinus node arrest), tachycardia, fibrillation, and cerebrovascular events (e.g. stroke, TIA, seizures). Persantine may cause severe hypotension and hot flushes. Diarrhoea has been observed.

Hypersensitivity reactions such as rash, urticaria, angio-oedema, laryngospasm, severe bronchospasm and very rarely anaphylactoid reactions have been reported.

ORAL ADMINISTRATION

Adverse reactions at therapeutic doses are usually minimal and transient. Occasionally diarrhoea, vomiting, headache, dizziness, nausea, flushing, syncope or weakness, myalgia, and skin rash have occurred during initiation of therapy. Mild occasional gastric distress can be avoided by administration of the tablets with a glass of milk. Gastric irritation, emesis and abdominal cramping may occur at high dosage levels. Rare cases of what appears to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy.

On those uncommon occasions when adverse reactions have been persistent or intolerable to the patient, withdrawal of the medication has been followed promptly by cessation of the undesirable symptoms.

When Persantine (dipyridamole) is used in combination with ASA, the only side effect clearly attributable to Persantine is headache. This symptom shows an increase of 5.5% in the combination treated group over that occurring in a group of patients treated with ASA alone. Other adverse reactions which occur during combination therapy are similar to those mentioned above, together with the well documented side effects of ASA therapy, notably gastric distress and gastrointestinal bleeding.

At the higher doses of Persantine there may be an increase in the incidence of adverse reactions.

In very rare cases, increased bleeding during or after surgery has been reported.

Post-Market Adverse Drug Reactions

As a result of its vasodilator properties, Persantine may cause hypotension, hot flushes, and tachycardia. Worsening of symptoms of coronary heart disease has been observed.
Hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angio-oedema have been reported.
Dipyridamole has been shown to be incorporated into gallstones (See Warnings).
Isolated cases of thrombocytopenia have been reported in conjunction with treatment with Persantine.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1- Established or Potential Drug-Drug Interactions

Persantine	Effect	Clinical comment
Persantine - Adenosine	Dipyridamole increases plasma levels and cardiovascular effects of adenosine.	Adjustment of adenosine dosage should be considered.
Persantine ampoules -Theophylline, aminophylline	The use of oral maintenance xanthines (e.g., theophylline, aminophylline) may abolish the coronary vasodilation produced by intravenous dipyridamole administration.	This could lead to false negative imaging results.
Persantine ampoules - Oral dipyridamole	In patients already receiving oral dipyridamole, clinical experience suggests that the sensitivity of the intravenous dipyridamole testing may be impaired.	Oral dipyridamole treatment should be discontinued for 24-hours prior to testing.
Persantine - Anticoagulants, thrombolytics	the combined use of such agents may result in an increased risk of hemorrhage.	Caution is necessary when dipyridamole is used concurrently with anticoagulants or thrombolytics.
Persantine - ASA	the addition of dipyridamole to acetylsalicylic acid does not increase the incidence of bleeding events.	
Persantine - Warfarin	When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.	
Persantine - Blood pressure lowering drugs	Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs.	

Persantine - Cholinesterase inhibitors	Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors.	In patients with myasthenia gravis, readjustment of therapy may be necessary during treatment with dipyridamole.

Drug-Food Interactions

Xanthine derivatives (e.g., found in coffee, tea) may weaken the effect of Persantine and therefore should be avoided 24 hours before myocardial imaging with Persantine.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ORAL ADMINISTRATION

Thromboembolic Disease

Recommended Dose and Dosage Adjustment

The recommended oral dose is 100 mg q.i.d., one hour before meals. The maximum daily dose is 600 mg. A lower dose of 100 mg of Persantine (dipyridamole) daily together with 1 g ASA daily, prolongs platelet survival to the same extent.

PARENTERAL ADMINISTRATION

Myocardial Perfusion Imaging

Recommended Dose and Dosage Adjustment

The dose of intravenous Persantine used as an adjunct to myocardial perfusion imaging should be adjusted according to the weight of the patient.

Immediately prior to infusion, Persantine i.v. should be diluted at least 1:2 with Dextrose Injection, USP 5%. The recommended dose is 0.142 mg/kg/min., infused over 4 minutes.

A total dose of greater than 60 mg is not recommended for use in any patient. The imaging agent should be injected within 5 minutes following the 4 minute infusion of Persantine. Do not mix i.v. Persantine with other drugs in the same syringe or infusion container. Infusion of undiluted Persantine may cause local irritation.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

OVERDOSAGE

Hypotension, if it occurs, is likely to be of short duration but vasopressor substances may be used if necessary. Symptoms such as feeling warm, flushes, sweating, accelerated pulse, restlessness, feeling of weakness and dizziness, and anginal complaints may occur. A drop in blood pressure

and tachycardia might be observed.

ORAL ADMINISTRATION
Symptomatic therapy is recommended. A gastric decontamination procedure should be considered. Administration of xanthine derivatives (e.g. aminophylline) may reverse the haemodynamic effects of dipyridamole overdose. Due to its wide distribution to tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

PARENTERAL ADMINISTRATION (I.V. INFUSION)
No cases of overdose in humans have been reported in this indication. Signs and symptoms as described under Side Effects are expected to occur. Aminophylline, as described in Warnings and Precautions may be administered. Due to its wide distribution to tissue and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Persantine (dipyridamole) normalizes increased platelet adhesiveness and tendency to aggregate (Hellem's Method).[4, 5] Persantine has been found to lengthen abnormally shortened platelet survival time in a dose-dependent manner; 400 mg/day or 100 mg/day plus 1 gram ASA.[15, 16, 17, 35, 36]

It is believed that platelet reactivity and interaction with prosthetic cardiac valve surfaces, resulting in abnormal shortened platelet survival time is a significant factor in connection with prosthetic heart valve replacement.

In a controlled clinical trial involving patients who had undergone surgical placement of prosthetic heart valves (mitral and/or aortic valve replacement), Persantine, in combination with anticoagulants, significantly decreased the incidence of post-operative thromboembolic events, without increasing hemorrhagic complications. The incidence of thromboembolic events in patients receiving dipyridamole in a dose of 400 mg/day in combination with anticoagulants was 1.3% compared to 14.3% to the control group treated with anticoagulant alone.[37, 38, 39]

In vitro dipyridamole potentiates the aggregation-inhibiting effects of adenosine and prostaglandin E_1, inhibits platelet uptake of adenosine, serotonin and glucose, and increases platelet cyclic AMP levels. At higher concentrations dipyridamole inhibits platelet aggregation induced by ADP or collagen.[1, 4, 29, 30, 33]

Myocardial blood flow increases in a dose-dependent fashion after i.v. or oral dipyridamole, with flows 170% or more above normal. Maximal increases are achieved at about 2.0 µg/mL with 0.8 µg/mL being the threshold serum level. Single oral doses of 150 mg dipyridamole produce the maximal response.[20, 21] At normal therapeutic doses, no significant alterations of peripheral blood flow, systemic blood pressure, or heart rate have been observed.

Pharmacodynamics

Persantine is a coronary vasodilator in man. The mechanism of vasodilation has not been fully elucidated, but may result from inhibition of uptake of adenosine, an important mediator of coronary vasodilation. The vasodilatory effects of Persantine are abolished by administration of the adenosine receptor antagonist theophylline.

How Persantine-induced vasodilation leads to abnormalities in thallium distribution (when administered intravenously for myocardial perfusion imaging) and ventricular function is also uncertain, but presumably represents a "steal" phenomenon. In this situation, relatively intact vessels dilate, and sustain enhanced flow, leaving reduced pressure and flow across areas of hemodynamically important coronary vascular constriction.

Pharmacokinetics

Absorption: Dipyridamole is readily absorbed from the gastrointestinal tract, reaching peak plasma levels in man 1-3 hours following oral administration.[22, 26, 29, 41] Peak plasma levels are dose-dependent and range from about 0.5 µg/mL after a 25 mg dose to 1.6 µg/mL after a 75 mg dose.[6, 29, 32, 41] Blood levels are quite variable, possibly depending on food intake and gastrointestinal peristalsis. Ingestion on an empty stomach may result in higher blood levels.[22, 32]

Distribution: Following intravenous administration, the distribution half-life in man is about 25 minutes[41] and after oral administration about 3 hours.[26, 29, 30] When plasma levels of drug are followed for up to 60 hours after i.v. or oral administration of 20 to 50 mg, plasma levels decline tri-exponentially with half-lives of 5 minutes (i.v. only), 53 minutes and about 10-12 hours.[22, 32] The volume of distribution is about 140 litres with about 92-99% binding to plasma proteins, primarily alpha1-acid glycoprotein.[22, 32]

STORAGE AND STABILITY

The Persantine Tablets should be stored at room temperature (15-30°C).
The Persantine Ampoule should be stored at room temperature (15-30°C).

SPECIAL HANDLING INSTRUCTIONS

Protect Persantine ampoules from direct light, and avoid freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

50 mg tablet: A coral-red, round, sugar-coated tablet, imprinted with the Ingelheim tower on one side.

75 mg tablet: A reddish-orange, round, sugar-coated tablet, imprinted with the Ingelheim tower on one side.

Persantine 50 mg and 75 mg are supplied in bottles of l00 tablets.

10 mL ampoules containing 5 mg/mL dipyridamole.
Persantine ampoules are supplied in packages of 5 ampoules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

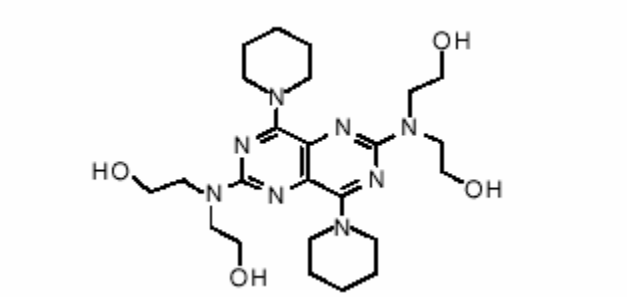
Drug Substance

Proper name: dipyridamole

Chemical name: 2,2',2",2'"-[(4,8-Dipiperidinolpyrimido[5,4-d]pyrimidine-2,6 diyl) dinitrilo]-tetraethanol

Molecular formula and molecular mass: $C_{24}H_{40}N_8O_4$ (504.6)

Structural formula:



Physicochemical properties:

Description: A homogeneous yellow crystalline powder, odourless but with a bitter taste. It is soluble in dilute acids, methanol, ethanol and chloroform. In solution, Persantine is yellow and shows a strong blue-green fluorescence.

Melting Range: 164-168°C

CLINICAL TRIALS

In a randomized, double-blind study, the effects of combined Persantine and ASA treatment were compared to ASA alone and to placebo in 2026 patients who had suffered a myocardial infarction 8 weeks to 5 years previously.[27, 28]

Combined treatment with Persantine 75 mg and ASA 325 mg t.i.d., reduced the life table rates for coronary incidence over a range of 37.0-66.7% when compared to placebo in the 4-24 month period after starting treatment. Similarly, for ASA alone, these reductions ranged from 29.1-51.4% over the same period. The differences between Persantine-ASA treatment and placebo

were statistically significant at each 4 monthly evaluation.

Differences between ASA alone and placebo were statistically significant only at 8 and 24 months. At the end of the follow-up, 41 months later, essentially no differences were found between ASA and Persantine-ASA treatment but both drug treated groups showed 21-25% lower coronary mortality and coronary incidence compared to placebo. This was no longer statistically significant.

Hospitalization longer than 2 weeks for recurrent myocardial infarction was significantly reduced in both drug treatment groups compared to the placebo group.

The patient subgroup (447 or about 20% of the total sample) entering the trial within 6 months after their last myocardial infarction showed the largest reduction in total and coronary mortality. However, the only statistically significant finding was a 63.6% reduction in life table rates for coronary death in the Persantine/ASA group compared to placebo after 36 months of treatment.

A randomized, double-blind trial comparing dipyridamole (begun two days before operation) plus ASA (begun seven hours after operation) against placebo, in 407 patients undergoing coronary bypass, showed a statistically significant reduction in the rate of graft occlusion in patients receiving dipyridamole and ASA.[7] Long-term follow-up showed that treatment with dipyridamole and ASA continued to be effective in preventing late development of vein graft occlusion after operation, and such treatment should be continued for at least one year.[8]
Use of Persantine pre-operatively in the prevention of bypass vein graft occlusion has not been associated with an increase of chest tube blood loss or transfusion requirements following coronary bypass surgery.[7]

DETAILED PHARMACOLOGY

Pharmacokinetics

In animal studies[23], autoradiography in rats shows the liver with the highest concentrations of dipyridamole, with decreasing quantities in the following tissues: adrenal cortex, kidneys, myocardium, pituitary, skeletal muscle, lungs and blood. Twice as much drug is found in the myocardium as in skeletal muscle. Within the myocardium, the largest portion of dipyridamole is intracellular with the sarcolemma fraction containing up to 50%. On the basis of autoradiography, there are only small amounts of placental transfer. The drug does not cross the blood-brain barrier.

Conjugation of dipyridamole with glucuronic acid is the primary pathway of metabolism. In individuals with surgical drainage of the biliary tract, 95% of an intravenous 25 mg dose can be recovered from the bile within 2 hours. Enterohepatic circulation has been demonstrated in both animals and man.[2]

Pharmacodynamics

Antithrombotic Effects:
The effects of dipyridamole on platelet function may be due to its inhibition of cyclic AMP-phosphodiesterase activity or to potentiation of the effect of prostacyclin. Both of these pathways would lead to an intracellular increase of cyclic AMP, which prevents platelet clumping.[25] Dipyridamole decreases platelet consumption and thrombosis associated with grafts and with the presence of foreign surfaces in the cardiovascular systems of experimental animals.[18, 19]

Teflon vascular prosthesis implanted in the superior vena cava of control dogs are coated with thrombotic deposits as early as 10 days following surgery. No thrombotic occlusions were observed 9 days or 6 months after surgery in dogs treated with dipyridamole 1 mg/kg/day, intravenously. At 18 months, prosthesis were coated with a thin layer of non-stenosing `neointima' without accumulation of thrombotic material.[18]

In primates, platelet survival shortened by arteriovenous cannulation or homocystine injection can be normalized by dipyridamole, 100 mg/day, or 25 mg/day plus 300 mg/day ASA. ASA alone had no effect. Decreased platelet counts in control pigs undergoing cardiopulmonary bypass are less pronounced if the animals are treated with dipyridamole 10 mg/kg.[1]

Thrombosis and neointimal fibrous hyperplasia (NFH) have been implicated as the major reasons for occlusion of the arterial grafts.[24] The operation causes intimal injury at the anastomotic site, promoting platelet adherence at this site or within the graft itself; it triggers platelet aggregation and eventual occlusion by a platelet-fibrin thrombus. In addition, fibrous hyperplasia is possibly induced by a platelet-derived growth factor (PDGF). In studies with dogs, treatment with dipyridamole (started before CABG surgery and continued post-operatively) with the addition of aspirin (begun after surgery) has been shown to be effective in preventing early platelet deposition on grafts,[14] early graft occlusion by thrombosis and possibly late graft narrowing by intimal hyperplasia.[24]

Circulatory Effects:
The effects of endogenous adenosine are potentiated by dipyridamole inhibition of adenosine uptake in erythrocytes and platelets.[4] Since adenosine is involved in physiological regulation of coronary blood flow, the coronary vasodilation induced by dipyridamole may be related to the adenosine-sparing effect of this drug.

Intravenous injection of dipyridamole in the dog causes coronary vasodilation.[3, 31] The threshold dose is 0.01 mg/kg with maximal effects reached by 0.2 mg/kg. A fall in systemic blood pressure, due to peripheral vasodilation, can be detected at a dose of 0.5 mg/kg with variable but not major effects on heart rate. The diastolic pressure decrease is larger than that for systolic pressure. The respiratory rate and depth are slightly increased, probably due to stimulation of carotid sinus chemoreceptors. An oral dose of 2.0 mg/kg in the dog increases coronary blood flow by 246% for 5 hours.[10]

In the presence of aneroid ring constriction of coronary vessels, chronic administration of dipyridamole in dogs, rabbits and pigs increases the number and diameter of collateral coronary vessels.[42] The rate of mortality in these animals is decreased compared to non-drug treated controls. Even in the absence of a chronic hypoxic stimulus, chronic dipyridamole treatment produces greater flow across intercoronary vessels in response to acute ligation of a coronary mainstem artery, compared to controls.[11, 31] When blood flow through ischemic areas was measured in experimentally produced infarctions, acute intravenous dipyridamole has produced both increases and decreases, as well as no change in flow.[3, 10, 20, 21] Intravenous dipyridamole, 10 mg/hr for 6 hours, decreased the size of experimental infarctions in dogs by 76% compared to saline-treated controls.[3]

TOXICOLOGY

Acute Toxicity of Dipyridamole, ASA and their Combination

Substance	Species	Route of Administration	LD_{50} (mg/kg)
dipyridamole	rat	p.o.	6,000
	rat	i.v.	200
	dog	p.o.	400
acetylsalicylic acid (ASA)	rat	p.o.	1,820
	dog	p.o.	1,000
dipyridamole/ASA*	mouse (male)	p.o.	3,000-5,000
	mouse (female)	p.o.	5,000
	rat (male)	p.o.	5,000
	rat (female)	p.o.	5,000
	mouse (male)	i.p.	910
	mouse (female)	i.p.	1,200
	rat (male)	i.p.	1,050
	rat (female)	i.p.	1,230
	dog	p.o.	875-950

*dipyridamole/ASA mixed in a ratio of 1/5, weight/weight

After administration of dipyridamole, signs of toxicity among the survivors were ataxia and depression, while in those that died; prostration and tonic convulsions were also seen. After ASA, lethargy fluctuating with restlessness, bleeding through the nose and respiratory distress occurred. Some animals died in a prostrate position without any preceding agitation.

Symptomatology following administration of the combination dipyridamole/ASA, (1/5), did not differ appreciably from the toxic signs observed with either substance alone.

Subacute intravenous administration of dipyridamole to dogs at levels of 1 and 10 mg/kg/day for 4 weeks did not produce significant signs of toxicity. Oral dipyridamole (20, 40, 60, 80 mg/kg/day) administered for 13 weeks to beagles produced no toxic effect at the low dose but resulted in kidney toxicity with increasing doses. This was manifested by weight loss, increased blood urea and serum creatinine and epithelial nephritis at the high dose. The abnormalities were rapidly reversible upon discontinuation of treatment. When dogs were treated orally for 26 weeks with dipyridamole at doses of 10, 20 and 40 mg/kg/day, only occasional emesis occurred at the high dose level. Hematological, biochemical and urinary analyses were within normal limits. Rats fed dipyridamole in the diet at levels of 25, 75 and 225 mg/kg/day over a period of 27 weeks showed no signs of toxicity.

Treatment of rats for 3 months with the combination dipyridamole/ASA (1/5) at oral doses of 25, 100 and 400 mg/kg resulted in no drug-related toxicity except for a delay in body weight development in the high dose group. In chronic toxicity studies of 6 months duration in rats and dogs, dipyridamole/ASA (1/4) had no toxic effect at doses of 25 and 100 mg/kg in either species.

With increasing dose (200 and 400 mg/kg/day), renal and gastrointestinal lesions appeared along with associated biochemical changes. At the high dose in dogs, all animals were dead at 3 months. Control groups of dogs received ASA, 80 and 160 mg/kg/day. The lesions observed were similar to toxic signs in the combination treatment groups except for the nephritis and renal changes seen in the 200 and 400 mg/kg dose groups of dogs.

Two year carcinogenicity studies of dipyridamole in mouse and rat in doses up to 75 mg/kg demonstrated no tumorogenic effect of the drug. The dipyridamole/ASA combination (1/5) also produced no evidence of carcinogenicity in either rats or mice at oral doses up to 450 mg/kg. Mutagenicity assays (cytogenetic, microorganism, dominant lethal and micronucleus tests) of both dipyridamole alone and the dipyridamole/ASA combination (1/15) could not demonstrate any mutagenic potential of these compounds.

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PART III: CONSUMER INFORMATION

Persantine
Dipyridamole

This leaflet is part III of a three-part "Product Monograph" published when Persantine was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Persantine. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Persantine tablets are indicated for the prevention of blood clot complications that can occur after prosthetic heart valve surgery.

What it does:
Persantine dilates the blood vessels of the heart muscle and regulates increased blood cell tendency to stick together. It works by preventing excessive blood clotting.

When it should not be used:
Persantine should not be used by patients with allergic reactions to dipyridamole or any component of the drug.

What the medicinal ingredient is:
Dipyridamole

What the important nonmedicinal ingredients are:
Acacia, calcium hydrogen phosphate, carnauba wax, colloidal silica, FDC yellow, magnesium stearate, polyethylene glycol, starch, sucrose, talc, titanium dioxide, white wax, and red iron oxide.

What dosage forms it comes in:
Persantine comes as a tablet to take by mouth. Tablets are 50 mg or 75 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use Persantine talk to your doctor or pharmacist:

- If you are allergic to dipyridamole or any other drug.
- If you are taking any other prescription or non prescription drugs, especially aspirin (ASA).
- If you have or ever had any heart problems, a low blood pressure or history of breathing problems.
- If you are pregnant, plan to become pregnant, or are breast-feeding. If you become pregnant while taking Persantine, call you doctor.
- If you are having surgery, including dental surgery, tell the doctor or dentist you are taking Persantine.

Worsening of symptoms of heart disease have been observed in some patients.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Persantine include: Adenosine, other drugs that prevent blood clotting, blood pressure lowering drugs, and cholinesterase inhibitors.

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dose is 100 mg taken four times daily, one hour before meals.
Sometimes a lower dose of 100 mg daily Persantine is taken together with 1.0 g of acetylsalicylic acid (ASA). Follow the directions given by your doctor carefully, and ask your doctor or pharmacist if you have any questions.

Overdose:
In case of overdose call you doctor immediately or call 911.

Missed Dose:
Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects from Persantine at prescribed doses are usually minimal and transient. Mild occasional stomach upset can be avoided by taking the tablets with glass of milk.
Tell your doctor if any of these symptoms are severe or do not go away after a while: dizziness, stomach pain, headache, rash, diarrhoea, vomiting, feeling warmth, or weakness.
If you experience any of the following call your doctor immediately: unusual bleeding or bruising, chest pain, increased heart rate, low blood pressure, or allergic reactions - difficulty breathing, severe bronchospasm or edema.

On rare occasions, when side effects have been persistent or intolerable stopping the medication has resolved the undesirable side effects. Do not stop taking the tablets without talking to your doctor.

Symptom / effect	Talk with your doctor or pharmacist	
	Only if severe or persistent	Call immediately in all cases
Dizziness, stomach pain, headache, rash, diarrhoea, vomiting, feeling warmth, weakness.	✓	
Unusual bleeding or bruising, chest pain, increased heart rate, low blood pressure, allergic reaction (difficulty breathing, severe bronchospasm or edema).		✓

This is not a complete list of side effects. For any unexpected effects while taking Persantine, contact your doctor or

pharmacist.

HOW TO STORE IT

Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature (15 – 30°C) and away from excess heat and moisture (not in the bathroom). Protect from light and freezing.
Do not let anyone else take your medication.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION
This document plus the full product monograph, prepared for health professionals can be found at:
http://www.boehringer-ingelheim.ca
or by contacting the sponsor, Boehringer Ingelheim Canada Ltd., at:1-800-263-5103, ext. 4633 (Medical Information)

This leaflet was prepared by Boehringer Ingelheim Canada Ltd.

Last revised: May DD, 2005.