PRODUCT MONOGRAPH

[Pr]Persantine®

Dipyridamole for Injection

5 mg/mL injectable ampoules

Coronary Vasodilator
Inhibitor of Platelet Adhesion and Aggregation

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[Pr]Persantine®

Dipyridamole for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
i.v. (intravenous)	10 mL ampoules, 5 mg/mL	Tartaric acid, polyethylene glycol, hydrochloric acid and sterile water for injection.

INDICATIONS AND CLINICAL USE

PERSANTINE (dipyridamole) is used intravenously 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 (dipyridamole) is not recommended in states of shock or collapse.

WARNINGS AND PRECAUTION

Since this drug may cause sudden death, cardiac arrest and ECG change, it should be only used in a clinical setting with appropriate equipment and under the monitoring of trained health professionals.

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 (see TOXICOLOGY).

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

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

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
Electrocardiogram Abnormalities/ST-T changes	7.5
Electrocardiogram Abnormalities/Extrasystoles	5.2
Hypotension	4.6
Nausea	4.6
Flushing	3.4
Electrocardiogram 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, electrocardiogram change,* arrhythmia unspecified, palpitation, ventricular tachycardia, bradycardia*, myocardial infarction*, AV block, syncope*, orthostatic hypotension, atrial fibrillation, ventricular 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.
*identified as adverse drug reactions based on master sheet

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 infarction, arrhythmias (including sinus arrest), tachycardia, fibrillation, and cerebrovascular events (including transient ischaemic attack, cerebrovascular accident, and convulsion). PERSANTINE may cause severe hypotension and hot flushes. Diarrhoea has been observed.

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

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1- Established or Potential Drug-Drug Interactions

PERSANTINE (dipyridamole)	Effect	Clinical comment
Adenosine	Dipyridamole increases plasma levels and cardiovascular effects of adenosine.	Adjustment of adenosine dosage should be considered.
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.
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.
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.
ASA	The addition of dipyridamole to acetylsalicylic acid does not increase the incidence of bleeding events.	

PERSANTINE (dipyridamole)	Effect	Clinical comment
Warfarin	When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.	
Blood pressure lowering drugs	Dipyridamole may increase the hypotensive effect of blood pressure lowering drugs.	Monitoring is advised.
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.

Drug-Lifestyle Interactions

Patients should be advised that they may experience undesirable effects such as dizziness during treatment with i.v. PERSANTINE. 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 24h after drug administration.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

In case of drug overdose, contact a health care practitioner, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

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.

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).[3] 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.[7, 8, 9, 17, 18]

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.[19, 20, 21]

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.[3, 12, 13, 16]

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. 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.[10, 12, 22] 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.[5, 19, 22, 29] Blood levels are quite variable, possibly depending on food intake and gastrointestinal peristalsis. Ingestion on an empty stomach may result in higher blood levels.[10, 15]

Distribution: Following intravenous administration, the distribution half-life in man is about 25 minutes[29] and after oral administration about 3 hours.[18, 19, 20] 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.[14, 22] The volume of distribution is about 140 litres with about 92-99% binding to plasma proteins, primarily alpha1-acid glycoprotein.[10, 15]

STORAGE AND STABILITY

The PERSANTINE ampoules 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

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

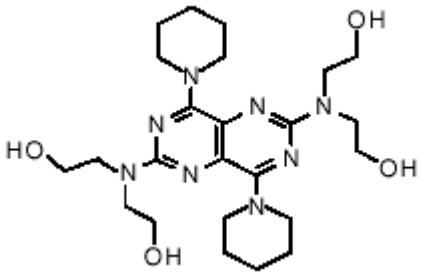
Drug Substance

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

DETAILED PHARMACOLOGY

Pharmacokinetics

In animal studies, [11] 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.[1]

Non-clinical data have also shown that dipyridamole can be excreted in breast milk.

Pharmacodynamics

Circulatory Effects:
The effects of endogenous adenosine are potentiated by dipyridamole inhibition of adenosine uptake in erythrocytes and platelets.[3] 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.[2, 14] 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.[5]

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.[23] 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.[6, 14] 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.[2, 5] Intravenous dipyridamole, 10 mg/hr for 6 hours, decreased the size of experimental infarctions in dogs by 76% compared to saline-treated controls.[2]

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.

Oral studies on reproduction toxicity did not reveal any embryo-/fetotoxic effects during organogenesis or in the perinatal phase. The NOELs for embryo/fetotoxicity were 40 mg/kg/day in rabbits, 125 mg/kg/day in mice and 1000 mg/kg/day in rats. In the perinatal study in rats doses exceeding 100 mg/kg/day showed an increased perinatal mortality and a reduced body weight development of the progeny. Fertility of rats was not impaired up to 1250 mg/kg/day. Autoradiographic investigations in rats showed that the progeny was exposed to the test compound in a low proportion of the dose. Reproductive toxicity of i.v. dipyridamole was not studied. It has been estimated that about 0.032% of an overall dose of dipyridamole of 25 mg is excreted in the breast milk of female rabbits.

Two year carcinogenicity studies of dipyridamole in mouse and rat in doses up to 75 mg/kg/day 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

[Pr]Persantine®
Dipyridamole for injection

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 ampoules for intravenous injection are used in a medical test (cardiac perfusion imaging) together with a radioactive substance to assess the flow of blood to the heart muscle. The test will help your doctor determine if there are areas of your heart which do not receive enough blood supply due to coronary artery disease.

Generally, cardiac perfusion imaging is done after an exercise/treadmill stress test. For patients who are unable to exercise adequately, the test is done after injection of PERSANTINE that mimics the effect of exercise on the heart.

What it does:
PERSANTINE dilates the blood vessels of the heart muscle and increases the blood flow to your heart.

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 non-medicinal ingredients are:
Tartaric acid, polyethylene glycol, hydrochloric acid and sterile water for injection.

What dosage forms it comes in:
PERSANTINE comes in 10 mL ampoules, containing 50 mg of dipyridamole.

WARNINGS AND PRECAUTIONS

Since this drug may cause sudden death, cardiac arrest and ECG change, it should be only used in a clinical setting with appropriate equipment and under the monitoring of trained health professionals.

BEFORE you use PERSANTINE talk to your doctor or pharmacist if:

- You are allergic to dipyridamole or any other ingredient in the drug.
- You have or ever had any heart problems, such as a recent heart attack (within the last 4 weeks), coronary artery disease, angina (chest pain) at rest, irregular heart beat, heart block (this usually causes a slow heart beat), heart failure or a problem affecting the heart valves.
- You have low blood pressure.
- You had a stroke or something called a transient ischemic attack (temporary stroke symptoms lasting less than 24 hours).
- You have breathing problems such as asthma, shortness of breath or wheezing.
- You have myasthenia gravis (a rare muscle problem).
- You are pregnant, likely to become pregnant, or are breast-feeding.

During the test, reactions similar to exercise-induced stress may occur; therefore your doctor will monitor you. Patients with a history of severe coronary heart disease or history of asthma may be at a greater risk. Abnormal heart beat, chest pain, bronchospasm or severe drop in blood pressure can occur. Your doctor may use another medication (aminophylline and nitroglycerin) to reverse these symptoms.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription and herbal medicines.

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

Tell your doctor about all medication that you are currently taking. Some medication may have to be stopped temporarily 24 hours before the test.

Theophylline or caffeine-containing drugs or food products and beverages (soft drinks, coffee, tea and chocolates) containing caffeine should be stopped 24 hours before the stress test.

PROPER USE OF THIS MEDICATION

Usual dose:
PERSANTINE ampoules are usually given as an injection by a doctor or nurse.

Another injection containing the imaging agent is given within 5 minutes of the PERSANTINE injection.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

No cases of overdose have been reported in this indication.
In case of overdose you may feel warm, flushes, sweating, accelerated pulse, restlessness, feeling of weakness and dizziness, and may have chest pain or difficulty breathing. A drop in blood pressure and fast heart rate might be observed. Your doctor may use another medication (aminophylline) to reverse these symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM
Like all medicines, PERSANTINE can cause side effects although not everybody gets them.

The following side effects have been observed during cardiac perfusion imaging with PERSANTINE. If you experience any of the following side effects, tell your doctor immediately:

Frequency	Symptom/effect
Very common	Headache
	Dizziness
	Chest pain/angina pectoris
Common	Tingling, prickling sensation
	Irregular heartbeat
	Rapid heartbeat
	Drop in blood pressure (feeling lightheaded, dizzy or faint)
	Hot flush (feeling intensive warmth with sweating and rapid heartbeats)
	Nausea
Uncommon	Heart attack
	Slow heartbeat
	Difficulty breathing, wheezing
	Abdominal pain
Rare	Excessive allergic reaction (symptoms could be itchy rash, swelling of lips, tongue and /or throat, runny nose, light headedness, headache, shortness of breath, hoarseness, cough and low blood pressure)
	Temporary symptoms of stroke
Very rare	Stroke
	Seizure
	Uncoordinated contraction of the cardiac muscle of the ventricles in the heart
Not known*	Swelling of the skin and the mucosa of the mouth and/or throat and tongue
	Fainting
	Temporary pause in the normal heart rhythm
	Impairment of the conduction between the atria and ventricles of the heart.
	Spasmodic closure of the voice box
	Diarrhea
	Vomiting
	Hives
	Rash
	Muscle pain

*A precise estimation of frequency is not possible as the adverse drug reactions did not occur in a clinical trial.

If you experience dizziness during the test, you should avoid potentially dangerous tasks such as driving or operating machines 24 hours after the test.

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

Protect PERSANTINE ampoules from direct light, and avoid freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**

Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

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. 84633 (Medical Information).

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd.

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