IV PERSANTINE®

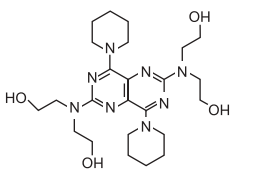
(dipyridamole USP) **For intravenous injection**

Prescribing Information

513113-1201

DESCRIPTION

Persantine® (dipyridamole USP) for intravenous injection is a coronary vasodilator described as 2,6-Bis(diethanolamino)-4,8-dipiperidinopyrimido [5,4-d]-pyrimidine. It has the following structural formula:



$C_{24}H_{40}N_8O_4$ Mol. Wt. 504.6

Dipyridamole in solution is an odorless, pale yellow liquid which can be diluted in normal saline and dextrose and water for intravenous administration.

IV Persantine® as a sterile solution for intravenous administration contains:

Active Ingredient VIAL 10 mL: dipyridamole USP 50 mg.

Inactive Ingredients VIAL 10 mL: polyethylene glycol 600 500 mg, tartaric acid 20 mg. pH is adjusted to 2.7 ± 0.5 with hydrochloric acid.

CLINICAL PHARMACOLOGY

In a study of 10 patients with angiographically normal or minimally stenosed (less than 25% luminal diameter narrowing) coronary vessels, IV Persantine® (dipyridamole USP) in a dose of 0.56 mg/kg infused over 4 minutes resulted in an average fivefold increase in coronary blood flow velocity compared to resting coronary flow velocity (range 3.8 to 7 times resting velocity). The mean time to peak flow velocity was 6.5 minutes from the start of the 4-minute infusion (range 2.5 to 8.7 minutes). Cardiovascular responses to the intravenous administration of Persantine® when given to patients in the supine position include a mild but significant increase in heart rate of approximately 20% and mild but significant decreases in both systolic and diastolic blood pressure of approximately 2-8%, with vital signs returning to baseline values in approximately 30 minutes.

Mechanism of Action

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 and ventricular function is also uncertain but presumably represents a "steal" phenomenon in which relatively intact vessels dilate, and sustain enhanced flow, leaving reduced pressure and flow across areas of hemodynamically important coronary vascular constriction.

Pharmacokinetics and Metabolism

Plasma dipyridamole concentrations decline in a triexponential fashion following intravenous infusion of Persantine®, with half-lives averaging 3-12 minutes, 33-62 minutes, and 11.6-15 hours. Two minutes following a 0.568 mg/kg dose of IV Persantine® administered as a 4-minute infusion, the mean dipyridamole serum concentration is 4.6±1.3 mcg/mL. The average plasma protein binding of dipyridamole is approximately 99%, primarily to α_1 -glycoprotein. Dipyridamole is metabolized in the liver to the glucuronic acid conjugate and excreted with the bile. The average total body clearance is 2.3-3.5 mL/min/kg, with an apparent volume of distribution at steady state of 1-2.5 L/kg and a central apparent volume of 3-5 liters.

INDICATIONS AND USAGE

IV Persantine® (dipyridamole USP) is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.

In a study of about 1100 patients who underwent coronary arteriography and IV Persantine® assisted thallium imaging, the results of both tests were interpreted blindly and the sensitivity and specificity of the Persantine® thallium study in predicting the angiographic outcome were calculated. The sensitivity of the Persantine® test (true positive Persantine® divided by the total number of patients with positive angiography) was about 85%. The specificity (true negative divided by the number of patients with negative angiograms) was about 50%.

In a subset of patients who had exercise thallium imaging as well as Persantine® thallium imaging, sensitivity and specificity of the two tests was almost identical.

CONTRAINDICATIONS

Hypersensitivity to dipyridamole or any of the other components of the drug.

WARNINGS

Serious adverse reactions associated with the administration of intravenous Persantine® (dipyridamole USP) have included cardiac death, fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, stroke, transient cerebral ischemia, seizures, anaphylactoid reaction, bronchospasm, severe hypotension, anaphylaxis with laryngospasm, and angioedema. There have been reported cases of asystole, sinus node arrest, sinus node depression and conduction block. Patients with abnormalities of cardiac impulse formation/conduction or severe coronary artery disease may be at increased risk for these events.

In a study of 3911 patients given intravenous Persantine® as an adjunct to thallium myocardial perfusion imaging, two types of serious adverse events were reported: 1) four cases of myocardial infarction (0.1%), two fatal (0.05%); and two non-fatal (0.05%); and 2) six cases of severe bronchospasm (0.2%). Although the incidence of these serious adverse events was small (0.3%, 10 of 3911), the potential clinical information to be gained through use of intravenous Persantine® thallium imaging (see Indications and Usage noting the rate of false positive and false negative results) must be weighed against the risk to the patient. Patients with a history of unstable angina may be at a greater risk for severe myocardial ischemia. Patients with a history of asthma may be at a greater risk for bronchospasm during IV Persantine® use.

When thallium myocardial perfusion imaging is performed with intravenous Persantine®, parenteral aminophylline should be readily available for relieving adverse events such as bronchospasm or chest pain. Vital signs should be monitored during, and for 10-15 minutes following, the intravenous infusion of Persantine® and an electrocardiographic tracing should be obtained using at least one chest lead. Should severe chest pain or bronchospasm occur, parenteral aminophylline may be administered by slow intravenous injection (50-100 mg over 30-60 seconds) in doses ranging from 50 to 250 mg. 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.

PRECAUTIONS See WARNINGS

Drug Interactions

Oral maintenance theophylline and other xanthine derivatives such as caffeine may abolish the coronary vasodilatation induced by intravenous Persantine® (dipyridamole USP) administration. This could lead to a false negative thallium imaging result (see Mechanism of Action).

Xanthine derivatives should be avoided 24 hours before myocardial imaging with IV Persantine.

Dipyridamole has been reported to increase the plasma levels and cardiovasular effects of adenosine. Adjustment of adenosine dosage may be necessary.

Myasthenia gravis patients receiving therapy with cholinesterase inhibitors may experience worsening of their disease in the presence of dipyridamole.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 111 week oral study in mice and in a 128-142 week oral study in rats, dipyridamole USP produced no significant carcinogenic effects at doses up to 75 mg/kg (0.8 times and 1.5 times the maximum recommended daily human oral dose on a mg/m^2 basis in mice and rats, respectively). Mutagenicity testing with dipyridamole was negative. Reproduction studies with dipyridamole revealed no evidence of impaired fertility in rats at dosages up to 500 mg/kg, or 10 times the maximum recommended human oral dose on a mg/m^2 basis. A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg (25 times the maximum recommended human oral dose on a mg/m^2 basis).

Pregnancy *Teratogenic Effects* PREGNANCY CATEGORY B

Reproduction studies have been performed in mice at doses up to 125 mg/kg, rats at doses up to 1000 mg/kg and rabbits at doses up to 40 mg/kg (1.3, 20, and 1.6 times the maximum recommended daily human oral dose on a mg/m^2 basis, respectively) and have revealed no evidence of harm to the fetus due to dipyridamole. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

As dipyridamole is excreted in human milk, caution should be exercised when IV Persantine® (dipyridamole USP) ia administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Adverse reaction information concerning intravenous Persantine® (dipyridamole USP) is derived from a study of 3911 patients in which intravenous Persantine® was used as an adjunct to thallium myocardial perfusion imaging and from spontaneous reports of adverse reactions and the published literature.

Serious adverse events (cardiac death, fatal and non-fatal myocardial infarction, ventricular fibrillation, asystole, sinus node arrest, symptomatic ventricular tachycardia, stroke, transient cerebral ischemia, seizures, anaphylactoid reaction, angioedema and bronchospasm) are described above (see WARNINGS).

In the study of 3911 patients, the most frequent adverse reactions were: chest pain/angina pectoris (19.7%), electrocardiographic changes (most commonly ST-T changes) (15.9%), headache (12.2%), and dizziness (11.8%).

Adverse reactions occuring in greater than 1% of the patients in the study are shown in Table 1:

Table 1 Drug-Related Adverse Reactions (%) Occurring in Greater than 1% of Patients

Adverse Reaction	Incidence (%) of Drug-Related Adverse Reactions
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 adverse reactions occurring in 1% or less of the patients within the study included:

Cardiovascular System: Electrocardiographic abnormalities (0.8%), arrhythmia (0.6%), palpitation (0.3%), ventricular tachycardia (0.2% see WARNINGS), bradycardia (0.2%), myocardial infarction (0.1% see WARNINGS), AV block (0.1%), syncope (0.1%), orthostatic hypotension (0.1%), atrial fibrillation (0.1%), supraventricular tachycardia (0.1%), ventricular arrhythmia (0.03% see WARNINGS), heart block (0.03%), cardiomyopathy (0.03%), edema (0.03%).

Central and Peripheral Nervous System: Hypothesia (0.5%), hypertonia (0.3%), nervousness/anxiety (0.2%), tremor (0.1%), abnormal coordination (0.03%), somnolence (0.03%), dysphonia (0.03%), migraine (0.03%), vertigo (0.03%).

Gastrointestinal System: Dyspepsia (1.0%), dry mouth (0.8%), abdominal pain (0.7%), flatulence (0.6%), vomiting (0.4%), eructation (0.1%), dysphagia (0.03%), tenesmus (0.03%), appetite increased (0.03%).

Respiratory System: Pharyngitis (0.3%), bronchospasm (0.2% see WARNINGS), hyperventilation (0.1%), rhinitis (0.1%), coughing (0.03%), pleural pain (0.03%).

Other: Myalgia (0.9%), back pain (0.6%), injection site reaction unspecified (0.4%), diaphoresis (0.4%), asthenia (0.3%), malaise (0.3%), arthralgia (0.3%), injection site pain (0.1%), rigor (0.1%), earache (0.1%), tinnitus (0.1%), vision abnormalities unspecified (0.1%), dysgeusia (0.1%), thirst (0.03%), depersonalization (0.03%), eye pain (0.03%), renal pain (0.03%), perineal pain (0.03%), breast pain (0.03%), intermittent claudication (0.03%), leg cramping (0.03%). In additional postmarketing experience, there have been rare reports of diarrhea, allergic reaction including urticaria, pruritus, dermatitis and rash. Mesenteric ischemia and mesenteric infarction have also been observed in association with intravenous Persantine® (dipyridamole USP) administration.

OVERDOSAGE

No cases of overdosage in humans have been reported. It is unlikely that overdosage will occur because of the nature of use (i.e., single intravenous administration in controlled settings).

Signs and symptoms as described under ADVERSE REACTIONS are expected to occur and could be even more severe in single cases.

Symptomatic therapy is recommended. Should severe chest pain or brochospasm occur, parenteral aminophylline may be administered by slow intravenous injection (50-100 mg over 30 to 60 seconds) in doses ranging from 50 to 250 mg.

See WARNINGS.

DOSAGE AND ADMINISTRATION

The dose of intravenous Persantine® (dipyridamole USP) as an adjunct to thallium myocardial perfusion imaging should be adjusted according to the weight of the patient. The recommended dose is 0.142 mg/kg/minute (0.57 mg/kg total) infused over 4 minutes. Although the maximum tolerated dose has not been determined, clinical experience suggests that a total dose beyond 60 mg is not needed for any patient.

Prior to intravenous administration, IV Persantine® should be diluted in at least a 1:2 ratio with 0.45% sodium chloride injection, 0.9% sodium chloride injection, or 5% dextrose injection for a total volume of approximately 20 to 50 mL. Infusion of undiluted Persantine® may cause local irritation.

Thallium-201 should be injected within 5 minutes following the 4-minute infusion of Persantine®.

Do not mix IV Persantine® with other drugs in the same syringe or infusion container.

Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

IV Persantine® (dipyridamole USP) for intravenous injection is available in boxes of five, ten and twenty vials.

Each 10 mL vial contains 50 mg of dipyridamole, NDC number 11994-005-05, 11994-005-10, 11994-005-20.

Store at 25°C (77°F); excursions permitted to 15-30°C (59°-86°F). [see USP Controlled Room Temperature]. Protect from direct light. Avoid freezing.

Rx only

Bristol-Myers Squibb
Medical Imaging, Inc.

Distributed by
Bristol-Myers Squibb
Medical Imaging, Inc.
N.Billerica, MA 01862

10 mL vial
Manufactured by
Bristol-Myers Squibb Holdings Pharma, Ltd.
Manati, Puerto Rico 00674

Boehringer Ingelheim

Licensed by
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

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Rev 7 Jan 2002

10 mL vial
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