DIPYRIDAMOLE INJECTION
For Intravenous Injection
Prescribing Information
Rx ONLY

DESCRIPTION
Diprydamole Injection is a coronary vasodilator described as 2,2'-2''-4,4'-diphosphonydiphenyl-2,5-dicyanodialkyl ethanolamine. It has the following structural formula:

\[
\text{Molecular Formula: } \text{C}_{22}\text{H}_{20}\text{N}_{4}\text{O}_{4}
\]

\[
\text{Molecular Weight: } 504.64
\]

Diprydamole injection is an odorless, pale yellow liquid which can be diluted in sodium chloride injection or dextrose injection for intravenous administration. Each mL of sterile solution contains Diprydamole, 5 mg. Polyethylene Glycol 600, 50 mg. Tartaric Acid, 2 mg. Water for Injection, Q5. Hydrochloric Acid and, if necessary, Sodium Hydroxide, added to adjust pH to 2.7 ± 0.5.

CLINICAL PHARMACOLOGY
In a study of 10 patients with angioarchitectural normol or minimally stenosed (less than 25% luminal diameter narrowing) coronary vessels, diprydamole injection in a dose of 0.56 mg/kg infused over 4 minutes resulted in an average twofold increase in coronary blood flow as compared to baseline flow, with no significant variation in peak flow velocity (range 3.9 to 7.8 mm/s). Cardiovascular responses to the intravenous administration of diprydamole 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% to 8%, with vital signs returning to baseline values in approximately 30 minutes.

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

Hypertension and infarction-induced vasodilatation leads to abnormalities in thallium distribution and ventricular function, and is a function of coronary disease. Tolerance of ventricular function and blood pressure is also a function of coronary disease. Tolerance and blood pressure are a function of ventricular function. In a large group of patients with coronary disease, the ventricular function and blood pressure of patients who do not exercise adequately.

In a study of about 1100 patients who underwent coronary angiography and diprydamole-assisted thallium imaging, the results of both tests were interpreted with reference to the severity and sensitivity of the thallium scintigraphy output in predicting the angiographic outcome. The sensitivity and specificity of the thallium scintigraphy test in predicting the angiographic outcome was about 85%. The specificity (true negative divided by the total number of patients with negative angiograms) was about 50%.

For a subset of patients who had exercise thallium imaging as well as diprydamole thallium imaging, sensitivity and specificity of the tests was almost identical.

CONTRAINDICATIONS

Hypersensitivity to diprydamole.

WARNINGS
Serious adverse reactions associated with the administration of intravenous diprydamole have included cardiac death, fatal and non-fatal myocardial infarction, ventricular arrhythmias, angina pectoris, and other coronary artery disease.

In a study of 3911 patients given intravenous diprydamole as an adjunct to thallium myocardial perfusion imaging, two types of serious adverse events were reported: four cases of myocardial infarction (0.1%), two fat (0.05%), and two non-fatal (0.05%) and 13 cases of severe bleeding complications. No cases of death or non-fatal myocardial infarction were attributed to these serious adverse events (0.3% of 10, 3911) the potential clinical information to be gained through use of intravenous diprydamole 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 pectoris should be monitored for adverse events such as brachychamia or chest pain. Vital signs should be monitored during, and for 10 to 15 minutes following, the intravenous injection of diprydamole and an electrocardiograph should be obtained at the end of the test. Should severe chest pain or brachychamia occur, parental amniphylline may be administered by slow intravenous injection (50 to 100 mg over 30 to 60 seconds) in doses ranging from 50 to 250 mg. In the case of severe hypotension the patient should be placed in an supine position with the head tilted down if necessary, before administration of parental amniphylline. If 250 mg of amniphylline does not resolve the hypotension within a few minutes, sublingual nitrogyrine may be administered. If chest pain continues despite use of amniphylline 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 parental amniphylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of amniphylline. This will allow initial thallium perfusion imaging to be performed before reversal of the pharmacologic effects of diprydamole on the coronary circulation.

PRECAUTIONS

See WARNINGS.

Drug Interactions: Oral maintenance theophylline and other xanthine derivatives such as caffeine may abolish the coronary vasodilation induced by intravenous diprydamole administration. This could lead to a false negative thallium imaging result (see CLINICAL PHARMACOLOGY, Mechanism of Action). Metycholine gravis patients receiving therapy with cholinesterase inhibitors may experience worsening of their disease in the presence of diprydamole.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In studies in which diprydamole was administered in the feed at doses of up to 75 mg/kg/day (4.9 times the maximum recommended daily human oral dose) in mice (up to 128 weeks males and up to 78 weeks in females) and rats (up to 128 weeks males and 104 weeks females), there was no evidence of drug related carcinogenicity. Mutagenicity tests of diprydamole with bacterial and mammalian cell systems were negative. There was no evidence of teratogenicity in mice when diprydamole was administered to male and female rats at oral doses up to 500 mg/kg/day (63 times the maximum recommended daily human oral dose). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg/day.

Calculation based on assumed body weight of 50 kg.

Pregnancy: Teratogenic Effects, Pregnancy Category B: Reproduction studies performed in mice and rats at oral doses of up to 125 mg/kg (15.6 times the maximum recommended daily human oral dose) administered daily at oral doses of up to 20 mg/kg (2.5 times the maximum recommended daily human oral dose) have revealed no evidence of impaired embryonic development due to
Adverse reactions occurring in greater than 1% of the patients in the study are shown in the following table:

<table>
<thead>
<tr>
<th>Incidence (%) of Drug-Related Adverse Events</th>
<th>Chest pain/angina pectoris</th>
<th>Headache</th>
<th>Dizziness</th>
<th>Electrocardiographic Abnormalities/ST-T changes</th>
<th>Hypotension</th>
<th>Nausea</th>
<th>Flushing</th>
<th>Electrocardiographic Abnormalities/Tachycardia</th>
<th>Dyspnea</th>
<th>Pain Unspecified</th>
<th>Blood Pressure Lability</th>
<th>Hypertension</th>
<th>Paresthesia</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain/angina pectoris</td>
<td>15.7</td>
<td>12.2</td>
<td>11.8</td>
<td>Electrocardiographic Abnormalities/Extrastyles</td>
<td>5.2</td>
<td>4.6</td>
<td>4.6</td>
<td>Electrocardiographic Abnormalities/Tachycardia</td>
<td>3.2</td>
<td>2.6</td>
<td>1.9</td>
<td>1.5</td>
<td>1.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Less common adverse reactions occurring in 1% or less of the patients within the study included:

Cardiovascular System: Electrocardiographic abnormalities unspecified (0.8%), arrhythmias unspecified (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 tachyarrhythmia unspecified (0.03% see WARNINGS), heart block unspecified (0.03%), cardiomyopathy (0.03%), edema (0.03%).

Central and Peripheral Nervous System: Hypnotisis (0.5%), hypothermia (0.3%), nervousness/irritability (0.2%), tremor (0.1%), abnormal coordination (0.03%), somnolence (0.03%), dysphoria (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 (0.9%), injection site reaction unspecified (0.4%), diaphoresis (0.4%), asthma (0.3%), malaise (0.3%), arthralgia (0.3%), injection site pain (0.1%), rigor (0.1%), earache (0.1%), sinusitis (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 addition to postmarketing experience, there have been rare reports of allergic reaction including urticaria, pruritus, dermatitis and rash.

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). See WARNINGS.

DOSE AND ADMINISTRATION
The dose of dipyradimole injection 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) injected 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, dipyradimole injection 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 dipyradimole injection may cause local irritation.

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

Do not mix dipyradimole injection with other drugs in the same syringe or infusion container.

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

HOW SUPPLIED
Dipyradimole for intravenous injection is available as follows:

Each 2 mL vial contains 10 mg of dipyradimole, NDC 55390-555-10; box of 10 vials.
Each 10 mL vial contains 50 mg of dipyradimole, NDC 55390-555-99; box of 10 vials.