DIPYRIDAMOLE- dipyridamole tablet, film coated
Lannett Company, Inc.

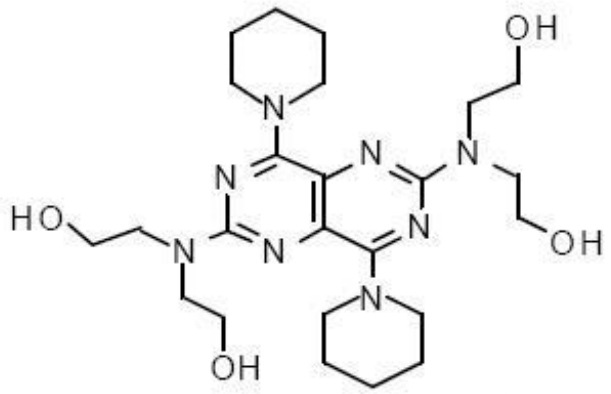
DIPYRIDAMOLE TABLETS, USP
25 mg, 50 mg, and 75 mg

Rx only

Prescribing Information

DESCRIPTION

Dipyridamole, USP is a platelet inhibitor chemically described as 2,2',2",2"'-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]-tetraethanol. It has the following structural formula:



$C_{24}H_{40}N_8O_4$ M.W. 504.63

Dipyridamole is an odorless yellow crystalline powder, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and practically insoluble in water.

Dipyridamole Tablets USP, 25 mg, 50 mg and 75 mg for oral administration contain 25 mg, 50 mg, and 75 mg of dipyridamole, USP, respectively.

Inactive ingredients for Dipyridamole Tablets USP, 25 mg, 50 mg, and 75 mg: microcrystalline cellulose, povidone, crospovidone, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, FD&C Red # 40 aluminum lake, FD&C Yellow #6 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

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

Dipyridamole tablets have been found to lengthen abnormally shortened platelet survival time in a dose-dependent manner.

In three randomized controlled clinical trials involving 854 patients who had undergone surgical placement of a prosthetic heart valve, dipyridamole tablets, in combination with warfarin, decreased the

incidence of postoperative thromboembolic events by 62 to 91% compared to warfarin treatment alone. The incidence of thromboembolic events in patients receiving the combination of dipyridamole tablets and warfarin ranged from 1.2 to 1.8%. In three additional studies involving 392 patients taking dipyridamole tablets and coumarin-like anticoagulants, the incidence of thromboembolic events ranged from 2.3 to 6.9%.

In these trials, the coumarin anticoagulant was begun between 24 hours and 4 days postoperatively, and the dipyridamole tablets were begun between 24 hours and 10 days postoperatively. The length of follow-up in these trials varied from 1 to 2 years.

Dipyridamole tablets do not influence prothrombin time or activity measurements when administered with warfarin.

Mechanism of Action

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes *in vitro* and *in vivo*; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5 to 1.9 mcg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A_2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP).

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3',5'-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

Hemodynamics

In dogs, intraduodenal doses of dipyridamole of 0.5 to 4.0 mg/kg produced dose-related decreases in systemic and coronary vascular resistance leading to decreases in systemic blood pressure and increases in coronary blood flow. Onset of action was in about 24 minutes and effects persisted for about 3 hours.

Similar effects were observed following IV dipyridamole in doses ranging from 0.025 to 2.0 mg/kg.

In man the same qualitative hemodynamic effects have been observed. However, acute intravenous administration of dipyridamole may worsen regional myocardial perfusion distal to partial occlusion of coronary arteries.

Pharmacokinetics and Metabolism

Following an oral dose of dipyridamole tablets, the average time to peak concentration is about 75 minutes. The decline in plasma concentration following a dose of dipyridamole tablets fits a two-compartment model. The alpha half-life (the initial decline following peak concentration) is approximately 40 minutes. The beta half-life (the terminal decline in plasma concentration) is approximately 10 hours. Dipyridamole is highly bound to plasma proteins. It is metabolized in the liver where it is conjugated as a glucuronide and excreted with the bile.

INDICATIONS AND USAGE

Dipyridamole Tablets, USP are indicated as an adjunct to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement.

CONTRAINDICATIONS

Hypersensitivity to dipyridamole and any of the other components.

PRECAUTIONS

General

Coronary Artery Disease

Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe coronary artery disease (e.g., unstable angina or recently sustained myocardial infarction). Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole.

Hepatic Insufficiency

Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.

Hypotension

Dipyridamole should be used with caution in patients with hypotension since it can produce peripheral vasodilation.

Laboratory Tests

Dipyridamole has been associated with elevated hepatic enzymes.

Drug Interactions

No pharmacokinetic drug-drug interaction studies were conducted with dipyridamole tablets. The following information was obtained from the literature.

Adenosine

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

Cholinesterase Inhibitors

Dipyridamole may counteract the antcholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies in which dipyridamole was administered in the feed to mice (up to 111 weeks in males and females) and rats (up to 128 weeks in males and up to 142 weeks in females), there was no evidence of drug-related carcinogenesis. The highest dose administered in these studies (75 mg/kg/day) was, on a mg/m^2 basis, about equivalent to the maximum recommended daily human oral dose (MRHD) in mice and about twice the MRHD in rats. Mutagenicity tests of dipyridamole with bacterial and mammalian cell systems were negative. There was no evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day (about 12 times the MRHD 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 (more than 30 times the MRHD on a mg/m^2 basis).

Pregnancy

Teratogenic Effects

PREGNANCY CATEGORY B

Reproduction studies have been performed in mice, rabbits and rats at oral dipyridamole doses of up to 125 mg/kg, 40 mg/kg and 1000 mg/kg, respectively (about 1 ½, 2 and 25 times the maximum recommended daily human oral dose, respectively, on a mg/m^2 basis) 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 response, dipyridamole should be used during pregnancy only if clearly needed.

Nursing Mothers

As dipyridamole is excreted in human milk, caution should be exercised when dipyridamole tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population below the age of 12 years have not been established.

ADVERSE REACTIONS

Adverse reactions at therapeutic doses are usually minimal and transient. On long-term use of dipyridamole tablets initial side effects usually disappear. The following reactions in Table 1 were reported in two heart valve replacement trials comparing dipyridamole tablets and warfarin therapy to either warfarin alone or warfarin and placebo:

Table 1. Adverse Reactions Reported in 2 Heart Valve Replacement Trials

Adverse Reaction	Dipyridamole Tablets/ Warfarin	Placebo/ Warfarin
Number of patients	**147**	**170**
Dizziness	13.6%	8.2%
Abdominal distress	6.1%	3.5%
Headache	2.3%	0.0%
Rash	2.3%	1.1%

Other reactions from uncontrolled studies include diarrhea, vomiting, flushing and pruritus. In addition, angina pectoris has been reported rarely and there have been rare reports of liver dysfunction. On those uncommon occasions when adverse reactions have been persistent or intolerable, they have ceased on withdrawal of the medication.

When dipyridamole tablets were administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone. In rare cases, increased bleeding during or after surgery has been observed.

In post-marketing reporting experience, there have been rare reports of hypersensitivity reactions (such as rash, urticaria, severe bronchospasm, and angioedema), larynx edema, fatigue, malaise, myalgia, arthritis, nausea, dyspepsia, paresthesia, hepatitis, thrombocytopenia, alopecia, cholelithiasis, hypotension, palpitation, and tachycardia.

OVERDOSAGE

In case of real or suspected overdose, seek medical attention or contact a Poison Control Center immediately. Careful medical management is essential. Based upon the known hemodynamic effects of dipyridamole, symptoms such as warm feeling, flushes, sweating, restlessness, feeling of weakness and dizziness may occur. A drop in blood pressure and tachycardia might also be observed.

Symptomatic treatment is recommended, possibly including a vasopressor drug. Gastric lavage should be considered. Administration of xanthine derivatives (e.g., aminophylline) may reverse the

hemodynamic effects of dipyridamole overdose. Since dipyridamole is highly protein bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Adjunctive Use in Prophylaxis of Thromboembolism after Cardiac Valve Replacement

The recommended dose is 75 to 100 mg four times daily as an adjunct to the usual warfarin therapy. Please note that aspirin is not to be administered concomitantly with coumarin anticoagulants.

HOW SUPPLIED

Dipyridamole Tablets USP, 25 mg are orange, round, film-coated tablets debossed "LCI" on one side and "1461" on the other side and are available in bottles of:

100 tablets	NDC 0527-1461-01
500 tablets	NDC 0527-1461-05
1000 tablets	NDC 0527-1461-10

Dipyridamole Tablets USP, 50 mg are orange, round, film-coated tablets debossed "LCI" on one side and "1462" on the other side and are available in bottles of:

100 tablets	NDC 0527-1462-01
500 tablets	NDC 0527-1462-05
1000 tablets	NDC 0527-1462-10

Dipyridamole Tablets USP, 75 mg are orange, round, film-coated tablets debossed "LCI" on one side and "1463" on the other side and are available in bottles of:

100 tablets	NDC 0527-1463-01
500 tablets	NDC 0527-1463-05
1000 tablets	NDC 0527-1463-10

Store at 20 to 25°C (68 to 77°F) [See USP Controlled Room Temperature].

KEEP OUT OF REACH OF CHILDREN.

Dispense in tight, light-resistant containers as defined in the USP.

Manufactured By:
Lannett Company, Inc.
Philadelphia, PA 19136

Rev. 01/08

PRINCIPAL DISPLAY PANEL

NDC 0527-1461-01

Lannett

DIPYRIDAMOLE TABLETS, USP

25 mg

Rx Only

100 TABLETS

NDC 0527-1462-01

Lannett

DIPYRIDAMOLE TABLETS, USP

50 mg

Rx Only

100 TABLETS

NDC 0527-1463-01

Lannett

DIPYRIDAMOLE TABLETS, USP

75 mg

Rx Only

100 TABLETS

DIPYRIDAMOLE

dipyridamole tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0527-1461
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DIPYRIDAMOLE (UNII: 64ALC7F90C) (DIPYRIDAMOLE - UNII:64ALC7F90C)	DIPYRIDAMOLE	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
CROSPOVIDONE (UNII: 2S7830E561)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ALUMINUM OXIDE (UNII: LMI26O6933)	

Product Characteristics			
Color	ORANGE	**Score**	no score
Shape	ROUND	**Size**	6mm

Flavor		**Imprint Code**	LCI;1461
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0527-1461-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	
2	NDC:0527-1461-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	
3	NDC:0527-1461-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040898	04/23/2008	

DIPYRIDAMOLE

dipyridamole tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0527-1462
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DIPYRIDAMOLE (UNII: 64ALC7F90C) (DIPYRIDAMOLE - UNII:64ALC7F90C)	DIPYRIDAMOLE	50 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
CROSPOVIDONE (UNII: 2S7830E561)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ALUMINUM OXIDE (UNII: LMI26O6933)	

Product Characteristics			
Color	ORANGE	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	LCI;1462
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0527-1462-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	
2	NDC:0527-1462-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	
3	NDC:0527-1462-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040898	04/23/2008	

DIPYRIDAMOLE

dipyridamole tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0527-1463
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DIPYRIDAMOLE (UNII: 64ALC7F90C) (DIPYRIDAMOLE - UNII:64ALC7F90C)	DIPYRIDAMOLE	75 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
CROSPOVIDONE (UNII: 2S7830E561)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	

TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ALUMINUM OXIDE (UNII: LMI26O6933)	

Product Characteristics			
Color	ORANGE	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	LCI;1463
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0527-1463-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	
2	NDC:0527-1463-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	
3	NDC:0527-1463-10	1000 in 1 BOTTLE; Type 0: Not a Combination Product	04/23/2008	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040898	04/23/2008	

Labeler - Lannett Company, Inc. (002277481)

Establishment

Name	Address	ID/FEI	Business Operations
Lannett Company, Inc.		829757603	ANALYSIS(0527-1461, 0527-1462, 0527-1463)

Revised: 11/2010 Lannett Company, Inc.