

DIPYRIDAMOLE- dipyridamole tablet
Global Pharmaceuticals, Division of Impax Laboratories Inc.

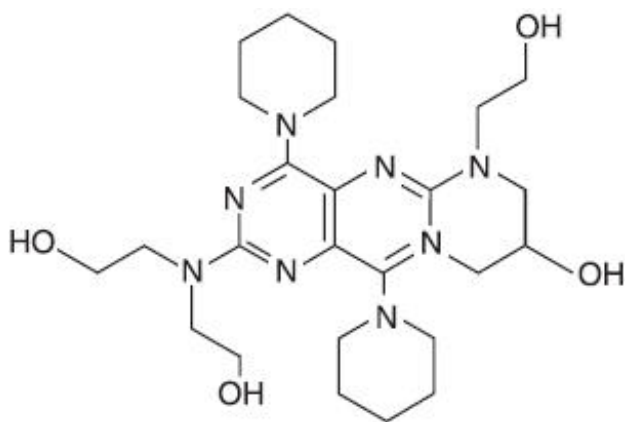
DIPYRIDAMOLE TABLETS USP
25 MG, 50 MG AND 75 MG

Rx only

PRESCRIBING INFORMATION

DESCRIPTION

Dipyridamole tablets are a platelet inhibitor chemically described as 2,2',2'',2'''-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]-tetraethanol. The molecular weight is 504.63 and the molecular formula is C₂₄H₄₀N₈O₄. The structural formula is represented below:



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.

Each tablet, for oral administration, contains 25 mg, 50 mg or 75 mg dipyridamole. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, pregelatinized starch, sodium starch glycolate, 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 µg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A₂-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 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 anticholinesterase 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/m² 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/m² 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/m² 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/m² 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 tablets 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 white to pale yellow, round, standard convex film-coated tablets debossed with "C81" on one side and plain on the other side.

Bottles of 100	NDC 0115-1070-01
Bottles of 1000	NDC 0115-1070-03

Dipyridamole Tablets USP, 50 mg are white to pale yellow, round, standard convex film-coated tablets debossed with "C82" on one side and plain on the other side.

Bottles of 100	NDC 0115-1071-01
Bottles of 1000	NDC 0115-1071-03

Dipyridamole Tablets USP, 75 mg are white to pale yellow, round, standard convex film-coated tablets debossed with "C83" on one side and plain on the other side.

Bottles of 100	NDC 0115-1072-01
Bottles of 1000	NDC 0115-1072-03

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

Dispense in a tightly-closed, light-resistant container (USP). Keep out of reach of children.

Rx only

Dist. By:
Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

657-02
Rev. 07/2013

PRINCIPAL DISPLAY PANEL - 25 mg Tablet Label

GLOBAL®

NDC 0115-1070-01

***Dipyridamole
Tablets, USP***

25 mg

Rx only

100 Tablets

GLOBAL[®]
 NDC 0115-1070-01
**Dipyridamole
 Tablets, USP**
25 mg
 Rx only
 100 Tablets

USUAL DOSAGE: See accompanying
 outsert for additional dosing
 information.
 Each tablet contains 25 mg of
 dipyridamole.
 Dispense in tightly-closed,
 light-resistant container as defined in
 the USP, with child-resistant closure,
 as required.
 Store at 20°C to 25°C (68°F to 77°F)
 [see USP Controlled Room
 Temperature].
**Do not use if printed
 safety seal under cap
 is broken or missing.**
 Keep this and all
 medication out of reach
 of children.

Dist. by:
 Global Pharmaceuticals
 Division of IMPAX Laboratories, Inc.
 Philadelphia, PA 19124 USA
 Product of Italy

3 01151 07001 1

653-02
 Rev. 05/2013
 Lot:
 Exp.:

PRINCIPAL DISPLAY PANEL - 50 mg Tablet Label

GLOBAL[®]
 NDC 0115-1071-01
**Dipyridamole
 Tablets, USP**
50 mg
 Rx only
 100 Tablets

GLOBAL[®]
 NDC 0115-1071-01
**Dipyridamole
 Tablets, USP**
50 mg
 Rx only
 100 Tablets

USUAL DOSAGE: See accompanying
 outsert for additional dosing information.
 Each tablet contains 50 mg of
 dipyridamole.
 Dispense in tightly-closed, light-resistant
 container as defined in the USP, with
 child-resistant closure, as required.
 Store at 20°C to 25°C (68°F to 77°F)
 [see USP Controlled Room
 Temperature].
**Do not use if printed safety
 seal under cap is broken
 or missing.**
 Keep this and all medication
 out of reach of children.

Dist. by:
 Global Pharmaceuticals
 Division of IMPAX Laboratories, Inc.
 Philadelphia, PA 19124 USA
 Product of Italy

3 01151 07101 8

655-02
 Rev. 05/2013
 Lot:
 Exp.:

PRINCIPAL DISPLAY PANEL - 75 mg Tablet Label

GLOBAL[®]
 NDC 0115-1072-01
**Dipyridamole
 Tablets, USP**
75 mg
 Rx only
 100 Tablets



NDC 0115-1072-01

Dipyridamole Tablets, USP

75 mg

Rx only
100 Tablets

USUAL DOSAGE: See accompanying
outsert for additional dosing information.
Each tablet contains 75 mg of
dipyridamole.

Dispense in tightly-closed, light-resistant
container as defined in the USP, with
child-resistant closure, as required.
Store at 20°C to 25°C (68°F to 77°F) [see
USP Controlled Room Temperature].

**Do not use if printed safety seal under
cap is broken or missing.**
Keep this and all medication out of reach of
children.

Dist. by: Global Pharmaceuticals
Division of IMPAX Laboratories, Inc.
Philadelphia, PA 19124 USA

Product of Italy

651-02
Rev. 05/2013



3 01151 07201 5

Lot:

Exp.:

DIPYRIDAMOLE

dipyridamole tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0115-1070
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
STARCH, CORN (UNII: O8232NY3SJ)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POVIDONES (UNII: FZ989GH94E)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	C81
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1070-01	100 in 1 BOTTLE		
2	NDC:0115-1070-03	1000 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040782	07/18/2007	

DIPYRIDAMOLE

dipyridamole tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0115-1071
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
STARCH, CORN (UNII: O8232NY3SJ)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POVIDONES (UNII: FZ989GH94E)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	C82
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1071-01	100 in 1 BOTTLE		
2	NDC:0115-1071-03	1000 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040782	07/18/2007	

DIPYRIDAMOLE

dipyridamole tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0115-1072
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
STARCH, CORN (UNII: O8232NY3SJ)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POVIDONES (UNII: FZ989GH94E)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	C83
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1072-01	100 in 1 BOTTLE		
2	NDC:0115-1072-03	1000 in 1 BOTTLE		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040782	07/18/2007	

Labeler - Global Pharmaceuticals, Division of Impax Laboratories Inc. (116732830)

Establishment

Name	Address	ID/FEI	Business Operations
Impax Laboratories Inc		790947167	MANUFACTURE(0115-1070, 0115-1071, 0115-1072)

Establishment

Name	Address	ID/FEI	Business Operations
Global Pharmaceuticals, Division of Impax Laboratories Inc.		116732830	REPACK(0115-1070, 0115-1071, 0115-1072)

Revised: 11/2013

Global Pharmaceuticals, Division of Impax Laboratories Inc.