DIPYRIDAMOLE- dipyridamole tablet, film coated AvKARE, Inc.

DIPYRIDAMOLE TABLETS USP 25 MG, 50 MG AND 75 MG

Rx only

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 <math>504.63 and the molecular formula is $C_{24}H_{40}N_8O_4$. 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 μ g/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 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 1/2, 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

	Dipyridamole	Placebo/
Adverse	Tablets/	Warfarin
Reaction	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 1000 NDC 42291-526-10

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 1000 NDC 42291-527-10

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 1000 NDC 42291-528-10

Store at 20° to 25°C (68° 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

Manufactured for:

AvKARE, Inc.

Pulaski, TN 38478

Mfg. Iss. 06/07 AV Rev. 12/12 (P)

PRINCIPAL DISPLAY PANEL

DIPYRIDAMOLE TABLETS 25MG

AvKARE

NDC 42291-526-10

Dipyridemole Tablets, USP

25 mg

1000 Tablets Rx Only

USUAL DOSAGE: See accompanying outsert for additional dosing information

Each tablet contains 25 mg of dipyridamole.

Dispense in a 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 - 77°F) [See USP Controlled Room Temperature].

Do not use if safety seal under cap is broken or missing.

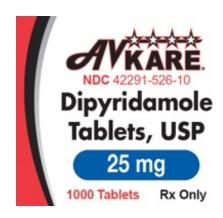
Keep this and all medication out of reach of children.

Manufactured for:

AvKARE, Inc.

Pulaski, TN 38478

Mfg. Iss. 06/07 AV Rev. 12/12 (P)



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

Do not use if safety seal under cap is broken or missing.

Keep this and all medication out of reach of children.

Manufactured for:

ANKARE, Inc.

Mfg. Iss. 06/07

Pulaski, TN 38478 AV Rev. 12/12 (P)

DIPYRIDAMOLE TABLETS 50MG

AvKARE

NDC 42291-527-10

Dipyridemole Tablets, USP

50 mg

1000 Tablets Rx Only

Each tablet contains:

Dipyridemole 50 mg

USUAL DOSAGE: See accompanying outsert for additional dosing information

Each tablet contains 50 mg of dipyridamole.

Dispense in a tightly-closed, light-resistant container as defined in the USP, with child-resistant closure, as required.

Do not use if safety seal under cap is broken or missing.

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

Do not use if safety seal under cap is broken or missing.

Keep this and all medication out of reach of children.

Manufactured for:

AvKARE, Inc.

Pulaski, TN 38478

Mfg. Iss. 06/07 AV Rev. 12/12 (P)

3 42291 52710 2



DIPYRIDAMOLE TABLETS 75MG

AVKARE

Dipyridemole Tablets, USP

75 mg

1000 Tablets RX Only

NDC 42291-528-10

Each tablet contains:

Dipyridemole 75 mg

USUAL DOSAGE: See accompanying outsert for additional dosing information.

Dispense in a tightly-closed, light-resistant container as defined in the USP, with child-resistant closure, as required.

Do not use if safety seal under cap is broken or missing.

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

Do not use if safety seal under cap is broken or missing.

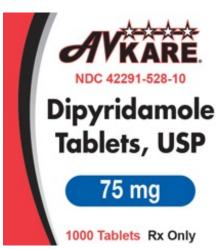
Keep this and all medication out of reach of children.

Manufactured for: **AvKARE**, **Inc.**

Pulaski, TN 38478

Mfg. Iss. 06/07 AV Rev. 12/12 (P)

₃ 42291 52710 ₂



USUAL DOSAGE: See accompanying outsert for additional dosing information.

Each tablet contains 75 mg of dipyridamole. Dispense in a tightly-closed, light-resistant container as defined in the USP, with child-resistant closure, as required.

Do not use if safety seal under cap is broken or missing. Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature].

Keep this and all medication out of reach of children.

Mfg. Rev. 06/07 AV Rev. 12/12 (P) Manufactured for:

DIPYRIDAMOLE

dipyridamole tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:42291- 526(NDC:0115-1070)
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety			
Ingredient Name Basis of Strength Strength			
DIPYRIDAMO LE (DIPYRIDAMO LE)	DIPYRIDAMOLE	25 mg	

Inactive Ingredients			
Ingredient Name	Strength		
SILICON DIO XIDE			
Hypromelloses			
LACTO SE MONO HYDRATE			
MAGNESIUM STEARATE			
Polyethylene Glycols			
POVIDONE			
STARCH, CORN			
SODIUM STARCH GLYCOLATE TYPE A POTATO			
TALC			
TITANIUM DIO XIDE			

Product Characteristics			
Color	YELLOW	Score	no score
Shape	ROUND	Size	5mm
Flavor		Imprint Code	C81
Contains			

P	ackaging			
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-526-10	1000 in 1 BOTTLE		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040782	07/08/2007	

DIPYRIDAMOLE

dipyridamole tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:42291- 527(NDC:0115-1071)
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
DIPYRIDAMO LE (DIPYRIDAMO LE)	DIPYRIDAMOLE	50 mg

Inactive Ingredients		
Ingredient Name	Strength	
SILICON DIO XIDE		
Hypromelloses		
LACTOSE MONOHYDRATE		
MAGNESIUM STEARATE		
Polyethylene Glycols		
POVIDONE		
STARCH, CORN		
SODIUM STARCH GLYCOLATE TYPE A POTATO		
TALC		
TITANIUM DIO XIDE		

Product Characteristics				
Color YELLOW Score no score				
Shape	ROUND	Size	8 mm	
Flavor		Imprint Code	C82	
Contains				

Packaging

1 NDC:42291-527-10	1000 in 1 BOTTLE			
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA040782	07/08/2007		

Marketing Start Date

Marketing End Date

Package Description

DIPYRIDAMOLE

Item Code

dipyridamole tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:42291- 528(NDC:0115-1072)
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
DIPYRIDAMO LE (DIPYRIDAMO LE)	DIPYRIDAMOLE	75 mg	

Inactive Ingredients		
Ingredient Name	Strength	
SILICON DIO XIDE		
Hypromelloses		
LACTOSE MONOHYDRATE		
MAGNESIUM STEARATE		
Polyethylene Glycols		
POVIDONE		
STARCH, CORN		
SODIUM STARCH GLYCOLATE TYPE A POTATO		
TALC		
TITANIUM DIO XIDE		

Product Characteristics			
Color	YELLOW	Score	no score
Shape	ROUND	Size	9 mm
Flavor		Imprint Code	C83
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-528-10	1000 in 1 BOTTLE		

Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA040782	07/08/2007		

Labeler - AvKARE, Inc. (796560394)

Revised: 3/2009 AvKARE, Inc.