

Doctor Leaflet

CARDOXIN FORTE

TABLETS

Composition

Active ingredient: each tablet contains: dipyridamole 75 mg

Inactive ingredients: Starch corn, silicon dioxide colloidal 200, starch soluble, magnesium stearate, calcium phosphate dibasic anhydrous, lactose monohydrate, hydroxypropylmethylcellulose, titanium dioxide, macrogol 4000, sunset yellow 85 (E110).

Each tablet contains approx. 2 mg lactose.

Action

Dipyridamole increases coronary blood flow and coronary sinus oxygen saturation. It appears to act predominantly on the small resistance vessels of the coronary vascular bed. The coronary vasodilator effect of dipyridamole is probably due to its ability to inhibit adenosine deaminase in the blood, thus allowing the accumulation of adenosine, a potent vasodilator. It may also cause vasodilation by inhibiting the enzyme phosphodiesterase, thus delaying the hydrolysis of cyclic adenosine monophosphate (cAMP).

In vitro models, induced-thrombotic animal models and several clinical studies have shown that the prophylactic administration of the proper dose of dipyridamole can, in many cases, reduce the number of thromboembolic episodes. This is based on its ability to prevent platelet adhesion and aggregation, thus prolonging platelet survival time.

It is postulated that dipyridamole acts by enhancing prostacyclin effects or inhibiting phosphodiesterase, thus increasing adenyl cyclase formation. It has also been shown to inhibit the formation of thromboxane-A₂, which is known to cause platelet adhesion and aggregation.

Indications

As an adjunct to oral anticoagulants for prophylaxis of thromboembolism associated with prosthetic heart valves.

Reduction of proteinuria in the nephrotic syndrome.

Treatment of membranoproliferative glomerulonephritis.

Prevention of pre-eclampsia in the final trimester of pregnancy.

Prevention of transplant artery stenosis.

Prevention of post-operative thromboembolic complications of coronary artery surgery.

In combination with acetylsalicylic acid in cases of recurrent deep vein thrombosis resistant to oral anticoagulants.

Prevention of thrombogenic manifestations.

As an alternative to exercise stress in thallium myocardial imaging, particularly in patients unable to exercise or in those for whom exercise may be contraindicated.

Contraindications

Hypersensitivity to dipyridamole or any of the ingredients of the product.

Warnings

Use in pregnancy

Reproduction studies have been performed in mice at doses up to 125 mg/kg (15.6 times the maximum recommended daily human dose), rats at doses up to 1000 mg/kg (125 times the maximum recommended daily human dose) and rabbits at doses up to 40 mg/kg (5 times the maximum recommended daily human dose) 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, this drug should be used during pregnancy only if clearly needed. Cardoxin Forte may be used for the prevention of pre-eclampsia in the final trimester of pregnancy. Do not use before the sixth month of pregnancy.

Use in Breastfeeding

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

Use in Pediatrics:

Safety and efficacy in children younger than 12 years of age have not been established.

Adverse Reactions

If these occur, it is usually during the early part of treatment. The vasodilating properties of dipyridamole may occasionally produce a vascular headache which normally disappears with long-term use. Vomiting, diarrhoea and symptoms such as dizziness, faintness, nausea, dyspepsia and myalgia have been observed.

As a result of its vasodilator properties, dipyridamole may cause hypotension, hot flushes and tachycardia. Worsening of symptoms of coronary heart disease such as angina and arrhythmias.

Hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angio-oedema have been reported.

In very rare cases, increased bleeding during or after surgery has been observed. Isolated cases of thrombocytopenia have been reported in conjunction with treatment with dipyridamole. Dipyridamole has been shown to be incorporated into gallstones.

Precautions

Among other properties, dipyridamole acts as a vasodilator. It should be used with caution in patients with severe coronary artery disease, including unstable angina and/or recent myocardial infarction, left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).

Patients being treated with regular oral doses of dipyridamole should not receive additional intravenous dipyridamole. Clinical experience suggests that patients being treated with oral dipyridamole who also require pharmacological stress testing with intravenous dipyridamole, should discontinue oral dipyridamole for twenty-four hours prior to stress testing.

In patients with myasthenia gravis, readjustment of therapy may be necessary after changes in dipyridamole dosage (see Drug Interactions).

Dipyridamole should be used with caution in patients with coagulation disorders.

Drug Interactions

Dipyridamole increases plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should be considered if use with dipyridamole is unavoidable.

There is evidence that the effects of acetylsalicylic acid and dipyridamole on platelet behaviour are additive.

The administration of antacids may reduce the efficacy of dipyridamole.

It is possible that dipyridamole may enhance the effects of oral anti-coagulants.

When dipyridamole is used in combination with anticoagulants and acetylsalicylic acid, the statements on intolerance and risks for these preparations must be observed. Addition of dipyridamole to acetylsalicylic acid does not increase the incidence of bleeding events. When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.

Dipyridamole may increase the hypotensive effect of drugs which reduce blood pressure and may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

Dosage and Administration

Dosage should be determined individually, according to the indication and severity of the clinical picture.

The oral dosage in adult patients is 150-375 mg, divided into 3 or 4 doses daily, taken with half a glass of water before meals. The maximum dosage is 600 mg daily.

Patients with Artificial Heart Valves

As an adjunct to oral anticoagulants for prophylaxis of thromboembolism associated with prosthetic heart valves, the recommended dosage is 75-150 mg 4 times daily.

Reduction of Proteinuria in Nephrotic Syndrome

The recommended oral dosage is 75 mg of dipyridamole 3-4 times daily (together with 325 mg acetylsalicylic acid daily).

Treatment of Membranoproliferative Glomerulonephritis

The recommended oral dosage is 75 mg of dipyridamole 3-4 times daily (together with 325 mg acetylsalicylic acid daily).

Prevention of Pre-eclampsia

To prevent pre-eclampsia in the final trimester of pregnancy, the recommended oral dosage is dipyridamole 300 mg daily. Do not use before the sixth month of pregnancy.

Prevention of Transplant Artery Stenosis

The recommended oral dosage is dipyridamole 75-375 mg daily.

Coronary Artery Surgery

The following is the recommended schedule for the prevention of post-operative thromboembolic complications of coronary artery surgery:

For two days prior to surgery, administer dipyridamole 75-150 mg orally 4 times daily.

In the morning of the day scheduled for surgery, administer an oral dose of dipyridamole 75-150 mg.

One hour after surgery, administer dipyridamole 75 mg down a nasogastric tube, and then clamp for 1 1/2 hours.

Seven hours after surgery, administer dipyridamole 75 mg and acetylsalicylic acid 325 mg down a nasogastric tube and then clamp for 1 1/2 hours.

On the day following surgery and thereafter, dipyridamole 75 mg and acetylsalicylic acid 325 mg should be taken orally 3 times daily.

Recurrent Deep Vein Thrombosis

In cases of recurrent deep vein thrombosis resistant to oral anticoagulants, the recommended dosage is 75 mg, 3 times daily, in combination with acetylsalicylic acid.

Prevention of Thrombogenic Manifestations

Dipyridamole 75 mg, 3 times daily.

Dosage in Thallium Imaging

Dipyridamole 300-400 mg orally.

Children

The normal total daily dosage is dipyridamole 5 mg/kg body weight, in divided doses.

Overdosage

Symptoms

Due to the low number of observations, experience with dipyridamole overdose is limited.

Symptoms such as a warm feeling, flushes, sweating, restlessness, feeling of weakness, dizziness and anginal complaints can be expected. A drop in blood pressure and tachycardia might be observed.

Treatment

Symptomatic therapy is recommended. Administration of xanthine derivatives (e.g. aminophylline) may reverse the haemodynamic effects of dipyridamole overdose. Due to its wide distribution to tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

Pharmacological properties

Pharmacodynamic properties

Dipyridamole has an antithrombotic action based on its ability to modify various aspects of platelet function, such as platelet aggregation, adhesion and survival, which have been shown to be factors associated with the initiation of thrombus formation. Dipyridamole also has coronary vasodilator properties.

Pharmacokinetic properties

After dosing with the sugar-coated tablets there is a lag time of 10 - 15 min associated with disintegration of the tablet and gastric emptying. Thereafter the drug is rapidly absorbed and peak plasma concentrations are attained after 1 hour. Geometric mean (range) peak plasma concentrations at steady state conditions with 75 mg t.d.s. were 1.86 µg/mL (1.23 - 3.27 µg/mL), and at trough were 0.13 µg/mL (0.06 - 0.26 µg/mL). With 75 mg q.i.d. corresponding peak concentrations were 1.54 µg/mL (0.975 - 2.17 µg/mL), trough concentrations were 0.269 µg/mL (0.168 - 0.547 µg/mL). With 100 mg q.i.d. corresponding peak concentrations were 2.36 µg/mL (1.13 - 3.81 µg/mL), trough concentrations were 0.432 µg/mL (0.186 - 1.38 µg/mL). The dose linearity of dipyridamole after single dose administration was demonstrated in the range from 25 to 150 mg.

Pharmacokinetic evaluations as well as experimental results in steady state conditions indicate that t.d.s. or q.d.s. dosage regimens are suitable. Treatment with dipyridamole tablets at steady state provides absolute bioavailability of approx. 60% and relative bioavailability of approx. 95% compared to an orally administered solution. This is partly due to a first-pass-effect from the liver which removes approx. 1/3 of the dose administered and partly to incomplete absorption.

Distribution

Owing to its high lipophilicity, log P 3.92 (n-octanol/0.1 N, NaOH), dipyridamole distributes to many organs.

Non-clinical studies indicate that, dipyridamole is distributed preferentially to the liver, then to the lungs, kidneys, spleen and heart, it does not cross the blood-brain barrier to a significant extent and shows a very low placental transfer. Non-clinical data have also shown that dipyridamole can be excreted in breast milk.

Protein binding of dipyridamole is about 97 - 99%, primarily it is bound to alpha 1-acid glycoprotein and albumin .

Metabolism

Metabolism of dipyridamole occurs in the liver. Dipyridamole is metabolized by conjugation with glucuronic acid to form mainly a monoglucuronide and only small amounts of diglucuronide. In plasma about 80% of the total amount is parent compound, 20% of the total amount is monoglucuronide with oral administration .

Elimination

Dominant half-lives ranging from 2.2 to 3 hours have been calculated after the administration of PERSANTIN. A prolonged terminal elimination half-life of approximately 15 h is observed. This terminal elimination phase is of relatively minor importance in that it represents a small proportion of the total AUC, as evidenced by the fact that steady-state is achieved within 2 days with both t.d.s. and q.d.s., regimens. There is no significant accumulation of the drug with repeated dosing. Renal excretion of parent compound is negligible (< 0.5%). Urinary excretion of the glucuronide metabolite is low (5%), the metabolites are mostly (about 95%) excreted via the bile into the faeces, with some evidence of entero-hepatic recirculation. Total clearance is approx. 250 mL/min and mean residence time is approx. 8 h (resulting from an intrinsic MRT of approx. 6.4 h and a mean time of absorption of 1.4 h).

Elderly subjects

Plasma concentrations (determined as AUC) in elderly subjects (> 65 years) were about 50% higher for tablet treatment and about 30% higher with intake of PERSANTIN 200 mg modified release capsules than in young (<55 years) subjects. The difference is caused mainly by reduced clearance; absorption appears to be similar. A similar increase in plasma concentrations in elderly patients was observed in the ESPS2 study.

Hepatic impairment

Patients with hepatic insufficiency show no change in plasma concentrations of dipyridamole, but an increase of (pharmacodynamically inactive) glucuronides. It is suggested to dose dipyridamole without restriction as long as there is no clinical evidence of liver failure.

Renal impairment

Since renal excretion is very low (5%), no change in pharmacokinetics is to be expected in cases of renal insufficiency. In the ESPS2 trial, in patients with creatinine clearances ranging from about 15 mL/min to >100 mL/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

Presentation

100 tablets.

Storage

Store below 25°C.

Rafa Laboratories Ltd. P O Box 405, Jerusalem 91003

Registration number: 0271921428

The format of this leaflet was determined by the Ministry of Health that checked and approved its content in June 2012.