PACKAGE INSERT
PERAZODIN

PRODUCT NAME

Perazodin 75 mg coated tablets

NAME AND STRENGTH OF ACTIVE SUBSTANCE

Each coated tablet contains 75 mg dipyridamole.

PRODUCT DESCRIPTION

Orange, round, sugar-coated tablets.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents
ATC code: B01AC07

Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells in vitro and in vivo; the inhibition amounts to 80% at its maximum and occurs dose- dependently at therapeutic concentrations (0.5-2 µg/mL). Consequently, there is an increased concentration of adenosine locally to act on the platelet A2-receptor, stimulating platelet adenylate cyclase, thereby increasing platelet cAMP levels. Thus, platelet aggregation in response to various stimuli such as PAF, collagen and ADP is inhibited. Reduced platelet aggregation reduces platelet consumption towards normal levels. In addition, adenosine has a vasodilator effect and this is one of the mechanisms by which dipyridamole produces vasodilation.

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. Whilst the inhibition of cAMP-PDE is weak, therapeutic levels inhibit cGMP-PDE, thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, identified as NO). Dipyridamole also stimulates the biosynthesis and release of prostacyclin by the endothelium. Dipyridamole reduces the thrombogenicity of subendothelial structures by increasing the concentration of the protective mediator 13-HODE (13-hydroxyoctadecadienic acid)

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 dipyridamole. 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 dipyridamole 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.

Preclinical safety data

Dipyridamole has been extensively investigated in animal models and no clinically significant findings have been observed at doses equivalent to therapeutic doses in humans.

CLINICAL PARTICULARS

Indications

An adjunct to oral anti-coagulation for prophylaxis of thrombo-embolism associated with
prosthetic heart valves.

Dosage and method of administration

Dosage

Adults

300-600 mg daily in three or four divided doses.

Children

Perazodin is not recommended for children.

Method of administration

Oral administration.

Perazodin should usually be taken before meals.

Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section List of excipients.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to section Warnings and Precautions) the use of the product is contraindicated.

Warnings and 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 Perazodin 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 drugs containing 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 section Interactions).

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

A small number of cases have been reported in

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which unconjugated dipyridamole was shown to be incorporated into gallstones to a variable extent (up to 70% by dry weight of stone). These patients were all elderly, had evidence of ascending cholangitis and had been treated with oral dipyridamole for a number of years. There is no evidence that dipyridamole was the initiating factor in causing gallstones to form in these patients. It is possible that bacterial deglucuronidation of conjugated dipyridamole in the bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

One coated tablet contains 71.33 mg sucrose, resulting in 428 mg sucrose per maximum recommended daily dose for adults. Patients with the rare hereditary conditions of fructose intolerance should not take this medicine.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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 aspirin and dipyridamole on platelet behaviour are additive.

The administration of antacids may reduce the efficacy of Perazodin. It is possible that

Perazodin may enhance the effects of oral anti-coagulants.

When dipyridamole is used in combination with any substances impacting coagulation such as anticoagulants and antiplatelets the safety profile for these medications 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.

Pregnancy and lactation

Pregnancy

There is inadequate evidence of safety in human pregnancy, but Perazodin has been used for many years without apparent ill-consequence. Animal studies have shown no hazard. Medicines should not be used in pregnancy, especially the first trimester unless the expected benefit is thought to outweigh the possible risk to the foetus.

Breast-feeding

Dipyridamole is excreted in breast milk at levels approximately 6% of the plasma concentration. Therefore Perazodin should only be used during lactation if considered essential by the physician.

Fertility

No studies on the effect on human fertility have been conducted with Perazodin. Non-clinical studies with dipyridamole did not indicate direct or indirect harmful effects with respect to fertility.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness during treatment with Perazodin. If patients experience dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

Adverse effects

Adverse effects at therapeutic doses are usually mild and transient.

The following side effects have been reported, frequencies have been assigned based on a clinical trial (ESPS-2) in which 1654 patients received dipyridamole alone.

Frequencies

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders	
Thrombocytopenia	Not known
Immune system disorders	
Hypersensitivity	Not known
Angioedema	Not known
Nervous system disorders	
Headache	Very common
Dizziness	Very common
Cardiac disorders	
Angina pectoris	Common
Tachycardia	Not known
Vascular disorders	
Hypotension	Not known
Hot flush	Not known
Respiratory, thoracic and mediastinal disorders	
Bronchospasm	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea	Very common
Vomiting	Common
Skin and subcutaneous tissue disorders	
Rash	Common
Urticaria	Not known
Musculoskeletal, connective tissue and bone disorders	
Myalgia	Common
Injury, poisoning and procedural complications	
Postprocedural haemorrhage	Not known
Operative haemorrhage	Not known

Dipyridamole has been shown to be incorporated into gallstones (please refer to section warnings and precautions).

Overdose

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.

Therapy

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.

PHARMACEUTICAL PARTICULARS

List of excipients

Core

Lactose monohydrate, povidone, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, talc, ethanol.

Coating

Hypromellose, macrogol 400, titanium dioxide, talc, gelatin, macrogol 6000, povidone, sucrose, calcium carbonate, ponceau 4R E124, quinoline yellow E104

Shelf life

36 months.

Storage Conditions

Do not store above 30 °C. Protect from light and moisture.

Keep out of the reach and sight of children.

Presentation

PVC/Aluminium blisters. Pack sizes of 20 and 1000 coated tablets.

Manufacturer

Remedica Ltd.

Aharnon Street, Limassol Industrial Estate, 3056 Limassol, Cyprus

Product registrant

Goldplus Universal Pte Ltd

103 Kallang Avenue #06-02, Singapore 339504

Date of revision of the text

Perazodin
03 / 10 / 2022
N.S.

Final Size: 157 x 322mm
Colours: Black

