SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Perazodin 100 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Perazodin 100 mg coated tablets: Each coated tablet contains 100 mg dipyridamole.

Excipient(s) with known effect
This product contains 53.6 mg lactose monohydrate and 95.099 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet.

White, round, coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
Adults:
300-600 mg daily in three or four doses.

Children:
Perazodin is not recommended for children.

Perazodin should usually be taken before meals.

Method of administration
Oral administration.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to 'Special warnings and precautions for use') the use of the product is contraindicated.

4.4 Special warnings and precautions for use

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 'Interaction with other medicinal products and other forms of interaction').

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

A small number of cases have been reported in 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.

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

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

This product contains sunset yellow FCF aluminium lake E110.
May cause allergic reactions.

This product contains sodium.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, 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 (please refer to section 5.3).

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 (please refer to section 5.3).

4.7 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.

4.8 Undesirable 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 < 1/10
Uncommon	≥ 1/1,000< 1/100
Rare	≥ 1/10,000< 1/1,000
Very rare	< 1/10,000
Not known	(cannot be estimated from the available data)

<u>Blood and lymphatic system disorders</u>	
thrombocytopenia	not known
<u>Immune system disorders</u>	
hypersensitivity	not known
angioedema	not known
<u>Nervous system disorders</u>	
headache	very common
dizziness	very common
<u>Cardiac disorders</u>	
angina pectoris	common
tachycardia	not known
<u>Vascular disorders</u>	
hypotension	not known
hot flush	not known
<u>Respiratory, thoracic and mediastinal disorders</u>	
bronchospasm	not known
<u>Gastrointestinal disorders</u>	
diarrhoea	very common
nausea	very common

vomiting	common

Skin and subcutaneous tissue disorders

rash	common
urticarial	not known

Musculoskeletal, connective tissue and bone disorders

myalgia	common

Injury, poisoning and procedural complications

post procedural haemorrhage	not known
operative haemorrhage	not known

Dipyridamole has been shown to be incorporated into gallstones (please refer to section 4.4 'Special warnings and precautions for use').

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Malta
ADR Reporting Website
www.medicinesauthority.gov.mt/adrportal

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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)

5.2 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 Perazodin. 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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Povidone
Cellulose, microcrystalline
Sodium starch glycolate (Type A)
Lactose monohydrate
Silica, colloidal anhydrous
Magnesium stearate
Talc

Coating
Gelatin
Macrogol 6000
Povidone
Sucrose
Talc
Calcium Carbonate
Macrogol 400
Titanium dioxide
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25°C. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters. Pack sizes of 30, 100 and 1000 coated tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

MA084/01702

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 29 December 2006
Date of latest renewal: 19 November 2013

10. DATE OF REVISION OF THE TEXT

12th December 2019