Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pyranistole 200 mg prolonged release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release capsule contains 200 mg dipyridamole.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

Each prolonged-release capsule contains yellow coloured pellets encapsulated in opaque, white hard gelatin capsule shells, dimension approximately 23 mm x 8 mm. Each capsule is imprinted with "RENATA" on the cap and "DPY 200" on the body with edible black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin.

4.2 Posology and method of administration

Posology

Adults, including the elderly:
The recommended dose is one capsule twice daily, usually one in the morning and one in the evening preferably with meals.

Paediatric population:
Pyranistole capsules 200 mg is not recommended for children.

Method of administration
For oral administration. The capsules should be swallowed whole without chewing to maintain prolonged release properties.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Among other properties, dipyridamole acts as a potent vasodilator. It should therefore 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 Pyranistole capsules 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 Interactions).

Pyranistole capsules 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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 blood pressure lowering drugs and may counteract the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

Pyranistole capsules should not be taken at the same time as alcohol, as alcohol may increase the rate of release of dipyridamole from the prolonged-release preparation.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is inadequate evidence of safety in human pregnancy, but dipyridamole has been used for many years without apparent ill-consequence. Animal studies have shown no hazard. Nevertheless, medicines should not be used in pregnancy, especially the first trimester unless the expected benefit is thought to outweigh the possible risk to the fetus (please refer to section 5.3).

Breast-feeding
Dipyridamole 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 dipyridamole. 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 dipyridamole. 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

System Organ Class	Frequency	MedDRA terms
Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system disorders	Not known	Hypersensitivity, angioedema
Nervous system disorders	Very common	Headache, dizziness
Cardiac disorders	Common	Angina pectoris
	Not known	Tachycardia
Vascular disorders	Not known	Hypotension, hot flush
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm
Gastrointestinal disorders	Very common	Diarrhoea, nausea
	Common	Vomiting
Skin and subcutaneous tissue disorders	Common	Rash
	Not known	Urticaria
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia
Injury, poisoning and procedural complications	Not known	Post procedural haemorrhage, operative haemorrhage

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
Due to the low number of observations, experience with dipyridamole overdose is limited. Symptoms such as feeling warm, flushes, sweating, accelerated pulse, restlessness, feeling of weakness, dizziness, drop in blood pressure and anginal complaints can be expected.

Therapy
Symptomatic therapy is recommended. Administration of xanthine derivatives (e.g. aminophylline) may reverse the haemodynamic effects of dipyridamole overdose. ECG monitoring is advised in such a situation. 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, platelet aggregation inhibitors excluding heparin,
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 A_2-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

Absorption
Peak plasma concentrations are reached about 2 - 3 hours after administration. Mean peak concentrations at steady state conditions with 150 mg b.d. are 1.43 µg/mL (range 0.705 - 2.75 µg/mL), trough levels are 0.351 µg/mL (range 0.200 - 0.741 µg/mL). With a daily dose of 400 mg, the corresponding peak concentrations are 1.98 µg/mL (range 1.01 - 3.99 µg/mL); trough concentrations are 0.53 µg/mL (range 0.18 - l.01 µg/mL). There is no clinically relevant effect of food on the pharmacokinetics of dipyridamole. The absolute bioavailability is about 70%.

As first pass removes approx. 1/3 of the dose administered, near to complete absorption of dipyridamole prolonged-release capsules can be assumed.

Various kinetic studies at steady state showed, that all pharmacokinetic parameters which are appropriate to characterise the pharmacokinetic properties of prolonged-release preparations are either equivalent or somewhat improved with dipyridamole prolonged-release capsules given b.i.d. compared to dipyridamole tablets administered t.d.s. /q.d.s.: Bioavailability is slightly greater, peak concentrations are similar; trough concentrations are considerably higher and peak trough fluctuation is reduced

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.

Biotransformation
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).

Linearity/non-linearity
The dose linearity of dipyridamole after oral b.i.d. administration of the prolonged release capsules containing 150 and 200 mg was demonstrated.

Elderly
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 prolonged 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

Capsule contents
Tartaric acid
Povidone
Co-povidone
Talc
Hypromellose
Simeticone emulsion (Simethicone, Cetyl Stearyl alcohol & Cetyl Stearyl alcohol ethoxylate, Sodium Benzoate, Purified Water)
Butylated methacrylate copolymer
Hypromellose phthalate
Stearic acid
Triacetin

Hard gelatin capsules
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years [for 60's and 100's pack size]
3 years [for 30's pack size]

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

HDPE bottles with child-resistant, polypropylene closures with a translucent inner liner. Each bottle pack contains either 1 or 2 silica gel bags plus a molecular sieve bag.

Bottle packs contain 30, 60 or 100 (2 x 50) capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited
12 Crowe Street
Dundalk
Co. Louth
A91 NN29
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22865/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of renewal: 18th May 2023

10 DATE OF REVISION OF THE TEXT

May 2026