SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dipyridamole Tablets 100mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Dipyridamole 100 mg

Also contains 96.0 mg of lactose and 107.20 mg of sucrose. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sugar-coated tablet

White biconvex sugar-coated tablets with 9.5 mm in diameter approximately and plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic heart valves.

4.2 Posology and method of administration

Posology

Adults:

300-600 mg daily in three or four doses.

Paediatric population:

Dipyridamole is not recommended for children.

Elderly:

As for adults.

Method of administration

Dipyridamole is taken by mouth, and should usually be taken before meals.

4.3 Contraindications

Hypersensitivity to the active substance 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 disease, including unstable angina and/or 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 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 4.5).

Dipyridamole tablets 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.

Dipyridamole contains lactose and sucrose. Patients with rare hereditary conditions of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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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. Dipyridamole should not be used in pregnancy, especially for the first trimester, unless the expected benefit is thought to outweigh any 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 Dipyridamole should only be used during breast-feeding 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 of 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.

Very common (≥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.

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 know

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 and connective tissue disorders:

Myalgia: Common

Injury, poisoning and medical procedures:

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Due to the low number of observations, experience with dipyridamole overdose is limited. Symptoms such as 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 heaptic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin,
ATC code: B 01 AC 07

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

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 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.

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

Lactose
Maize starch
Povidone
Pregelatinised starch
Magnesium stearate
Bleached shellac
Sucrose
Talc
Titanium dioxide E171
Beeswax
Carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Containers: 36 months

Blister packs: 36 months

6.4 Special precautions for storage

Containers: Do not store above 25°C. Keep the container tightly closed.
Blister packs: Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polypropylene or high density polystyrene with polythene closure and polyurethane wads or polythene inserts.

Packs of 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000.

PVC/Aluminium foil blister packs 250 micron PVC glass-clear bluish rigid PVC (Pharmaceutical grade). 20 micron hard-tempered aluminium foil coated on the dull side with 6-7 gsm heat-seal lacquer and printed on the bright side.

Packs of 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000.

6.6 Special precautions for disposal and other handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Genethics Europe Limited

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Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 42976/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/12/2005

10 DATE OF REVISION OF THE TEXT

15/03/2023