

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dipyridamole 200mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral suspension contains 200mg dipyridamole.

Excipients with known effect:

Each 5ml of oral suspension contains 9mg of methyl parahydroxybenzoate (E218), 0.9mg of propyl parahydroxybenzoate (E216), 2040mg of liquid maltitol (E965) and 545.20mg of propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension

Yellow coloured suspension with orange flavor

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

Adults:

300-600mg (7.5-15ml) daily in three or four doses.

Children:

Dipyridamole is not recommended for children.

Dipyridamole should usually be taken before meals.

Method of administration:

For oral use only.

Shake well before use.

4.3 Contraindications

Hypersensitivity to Dipyridamole or 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 section 4.4) 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 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 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 (upto 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.

Excipients in the formulation

Dipyridamole oral suspension contains liquid maltitol (E965). Patients with a rare hereditary problem of fructose intolerance should not take this medicine.

The medicine also contains methyl (E218) and propyl parahydroxybenzoates (E216) which may cause allergic reactions (possibly delayed).

This medicine also contains 545.20mg/5ml of propylene glycol (E1520) as an ingredient necessary for the medicine to work properly.

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 Dipyridamole. It is possible that Dipyridamole 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. When dipyridamole was administered in patients with non-cardioembolic ischaemic stroke, treatment with triple antiplatelet therapy (aspirin + clopidogrel + dipyridamole) for secondary stroke prevention was associated with more bleeding and bleeding of greater severity, without any improvement in outcome.

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 Dipyridamole 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).

Lactation

Dipyridamole is excreted in breast milk at levels approximately 6% of the plasma concentration. Therefore 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.

Body Organ System	Very common ≥ 1/10	Common ≥ 1/100 < 1/10	Not known
<i>Blood and lymphatic system disorders</i>			Thrombocytopenia
<i>Immune system disorders</i>			Hypersensitivity Angioedema
<i>Nervous system disorders</i>	Headache Dizziness		
<i>Cardiac disorders</i>		Angina pectoris	Tachycardia
<i>Vascular disorders</i>			Hypotension Hot flush
<i>Respiratory, thoracic and mediastinal disorders</i>			Bronchospasm
<i>Gastrointestinal disorders</i>	Diarrhoea Nausea	Vomiting	
<i>Skin and subcutaneous tissue disorders</i>		Rash	Urticaria
<i>Musculoskeletal, connective tissue and bone disorders</i>		Myalgia	
<i>Injury, poisoning and procedural complications</i>			Post procedural haemorrhage, operative haemorrhage

Dipyridamole has been shown to be incorporated into gallstones (please refer to section 4.4).

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 in UK.

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: Anti-thrombotic, 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

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 metabolised 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.

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

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Polysorbate 80 (E433)

Simeticone emulsion 30% (containing polydimethylsiloxane, sorbitan monostearate, polyoxyethylene 20 sorbitan, silicon dioxide, xanthan gum, benzoic acid, sorbic acid, potassium hydroxide, hydrogen chloride and deionised water)

Liquid maltitol (E965)

Xanthan gum (E415)
Aluminium magnesium silicate (E553a)
Citric acid monohydrate (E330)
Disodium phosphate anhydrous (E339)
Ammonium glycyrrhizinate
Propylene glycol (E1520)
Orange flavour (containing propylene glycol (E1520))
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months.

Discard after 60 days of first opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bottle: Ph.Eur Type III Amber glass

Closure: Tamper evident, child resistant, plastic (Polypropylene/Polyethylene) cap with an EPE liner.

Dosing Device: Double ended white polypropylene plastic spoon with 2.5ml and 5ml measuring ends.

Pack size: 150ml and 300ml

Not all pack sizes may be marketed

6.6 Special precautions for disposal

This product may settle during storage. Shake the bottle well before use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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AUTHORISATION**

06/01/2016

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04/12/2020