Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dipyridamole 50 mg/5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains Dipyridamole 50 mg

Excipients with known effect:
Each 5 ml contains 2.80 g liquid maltitol (E965), 2.01 mg ethyl parahydroxybenzoate (E214), 1.34 mg propyl parahydroxybenzoate (E216) and 9.15 mg methyl parahydroxybenzoate (E218).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Suspension

Yellow sugar free suspension with a banana odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dipyridamole 50 mg/5 ml Oral Suspension is indicated in adults 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 to four doses.

Paediatric population

The safety and efficacy of Dipyridamole in children have not been established.
Dipyridamole is not recommended for children.

Method of administration

Dipyridamole 50 mg/5 ml Oral Suspension should usually be taken before meals.

This product may settle during storage. Please shake the bottle thoroughly before use.

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 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 doses of Dipyridamole 50 mg/5 ml Oral Suspension should not receive additional intravenous dipyridamole. If pharmacological stress testing with intravenous dipyridamole for coronary heart disease is considered necessary, then oral dipyridamole should be discontinued twenty-four hours prior to testing.

In patients with myasthenia gravis, readjustment of therapy may be necessary after changes in dipyridamole dosage (see Drug Interactions).

Dipyridamole 50 mg/5 ml Oral Suspension should be used in caution with 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 bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

Dipyridamole 50 mg/5 ml Oral Suspension contains liquid maltitol (E965). Patients with rare hereditary problems of fructose intolerance should not take this medicine. Dipyridamole 50 mg/5 ml Oral Suspension contains 2.8 g maltitol per 5 ml of suspension and may have a mild laxative effect. Maltitol has a calorific value of 2.3 kcal/g.

Dipyridamole 50 mg/5 ml Oral Suspension contains methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and ethyl parahydroxybenzoate (E214) which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Dipyridamole increases plasma level 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 anticoagulants and acetylsalicylic acid, the statements on intolerance and risks for these preparations 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 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 in 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 of 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

None stated.

4.8 Undesirable effects

If these occur, it is usually during the early part of the treatment. The vasodilating properties of dipyridamole may occasionally produce a vascular headache which normally disappears with long term use. Vomiting, diarrhoea and symptoms such as dizziness, faintness, nausea, dyspepsia and myalgia have been observed.

As a result of its vasodilator properties, dipyridamole may cause hypotension, hot flushes and tachycardia. Worsening of symptoms of coronary heart disease such as angina and arrhythmias.

Hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angio-oedema have been reported.
In very rare cases, increased bleeding during or after surgery has been observed. Isolated cases of thrombocytopenia have been reported in conjunction with treatment with dipyridamole.
Dipyridamole has been shown to be incorporated into gallstones.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie. By reporting side effects you can help provide more information on the safety of this medicine.

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 may be expected. A drop in blood pressure and tachycardia might be observed.

Therapy
Symptomatic therapy is recommended. A gastric decontamination procedure should be considered. 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

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

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.

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

Xanthan gum (E415)
Liquid maltitol (E965)
Disodium phosphate do-decahydrate
Saccharin sodium (E954)
Polysorbate 80 (E433)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Ethyl parahydroxybenzoate (E214)
Propylene glycol (E1518)
Citric acid monohydrate
Purified water
Magnesium aluminium silicate
Glycerol (E422)
Simeticone emulsion
Banana flavouring liquid.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 24 months

After first opening: Use within 30 days of first opening

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pharmaceutical grade III amber glass bottles with polypropylene child resistant closure with LDPE liner.

Pack sizes: 150 ml

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/149/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd May 2014

10 DATE OF REVISION OF THE TEXT