Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Persantin Retard 200 mg Modified Release Capsules, Hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains dipyridamole 200 mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified release capsules, hard.
Hard gelatin capsules consisting of a red cap and an orange body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Secondary prevention of ischaemic stroke and transient ischaemic attacks either alone or in conjunction with aspirin.
As an adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic heart valves.

4.2 Posology and method of administration

Adults, including the Elderly
One capsule twice daily, usually one in the morning and one in the evening, preferably with meals.
The capsules should be swallowed whole without chewing.
Children
Persantin Retard is not suitable for use in children.

4.3 Contraindications

Hypersensitivity to any components of the product.

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 recent myocardial infarction, left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).

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. Failure to do so may impair the sensitivity of the test.

In patients with myasthenia gravis, readjustment of therapy may be necessary during treatment with dipyridamole. (See Section 4.5 Interactions with other medicinal products and other forms of interaction).

PERSANTIN 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 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.

It is possible that dipyridamole may enhance the effects of oral anti-coagulants.

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

When dipyridamole is used in combination with any substances impacting coagulation such as anti-coagulants and antiplatelets, the safety profile for these medications must be observed.

Addition of dipyridamole to aspirin 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.

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 foetus (please refer to section 5.3)

Lactation
Persantin Retard 200 mg 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 PERSANTIN. Non-clinical studies with dipyridamole did not indicate direct or indirect harmful effects with respect to the fertility index (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 PERSANTIN. 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

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 known
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, 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 (see 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: 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 and dizziness, drop in blood pressure and anginal complaints may occur.

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 (cyclic adenosine monophosphate) levels. Thus, platelet aggregation in response to various stimuli such as PAF (platelet activating Factor), collagen and ADP (adenosine diphosphate) 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 (cyclic guanosine monophosphate)-PDE, thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, identified as NO (nitric oxide).

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

For long-term treatments PERSANTIN modified release capsules, formulated as pellets have been developed. The pH dependent solubility of PERSANTIN which prevents dissolution in the lower parts of the gastrointestinal tract is overcome by means of a formula containing tartaric acid. Retardation of release is achieved by a diffusion membrane which is sprayed onto the pellets.

Absorption
PERSANTIN modified release capsules
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 PERSANTIN 200 mg modified release capsules. The absolute bioavailability is about 70% . The dose linearity of dipyridamole after oral b.i.d. administration of the modified release capsules containing 150 and 200 mg was demonstrated .

As first pass removes approx. 1/3 of the dose administered, near to complete absorption of PERSANTIN modified

release capsules can be assumed.

Various pharmacokinetic studies showed, that all pharmacokinetic parameters at steady state which are appropriate to characterise the pharmacokinetic properties of modified release preparations are either equivalent or somewhat improved with dipyridamole modified 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 .

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 mean residence time (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

Tartaric acid
Acacia
Povidone
Eudragit S 100 [methacrylic acid- methyl methacrylate copolymer (1:2)]
Hypromellose phthalate
Hypromellose
Triacetin
Talc
Dimethicone 350
Stearic acid
Capsule shell
Gelatin
Titanium dioxide E171
Red and Yellow iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: Three years.

In use: Discard any capsules remaining 6 weeks after first opening.

6.4 Special precautions for storage

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

Store below 30°C.

6.5 Nature and contents of container

White polypropylene bottles with child-resistant multi-part polypropylene/polyethylene plastic screw cap containing a desiccant made from silica gel/molecular sieves agent.
Packs containing 30 or 60 capsules are registered.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Ltd.
Ellesfield Avenue
Bracknell
Berkshire
RG12 8YS

United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0007/008/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 1998
Date of last renewal: 28th August 2008

10 DATE OF REVISION OF THE TEXT

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