IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1151/128/001
Case No: 2067641

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Asasantin Retard 200mg/25mg Modified Release Hard Capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **27/11/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Asasantin Retard 200mg/25mg Modified Release Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains dipyridamole 200mg and acetylsalicylic acid (aspirin) 25mg

Excipients-Contains Lactose monohydrate and sucrose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule containing acetylsalicylic acid in standard release form and dipyridamole in modified release form.

Product imported from the UK:
Capsules consisting of a red cap with no markings and an ivory body imprinted with the company logo and “01A”

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Secondary prevention of ischaemic stroke and transient ischaemic attacks.

4.2 Posology and method of administration

For oral administration.

The recommended dose is 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 together with a glass of water.

ASASANTIN Retard is not indicated for use in children and young people less than 16 years of age (see “Special Warnings and Precautions for Use”).

Alternative regimen in case of intolerable headaches
In the event of intolerable headaches during treatment initiation, switch to one capsule at bedtime and low-dose acetylsalicylic acid (ASA) in the morning. Because there are no outcome data with this regimen and headaches become less of a problem as treatment continues, patients should return to the usual regimen as soon as possible, usually within one week.

4.3 Contraindications

Hypersensitivity to any component of the product or salicylates.

Patients with active gastric or duodenal ulcers or bleeding disorders.

Patients in the last trimester of pregnancy.

In certain rare hereditary conditions the product is contraindicated owing to the presence of certain excipients in the product. (Refer to Special Warnings and Precautions for details).

4.4 Special warnings and precautions for use

Due to the risk of bleeding, as with other antiplatelet agents, ASASANTIN should be used with caution in patients at increased bleeding risk and patients should be followed carefully for any signs of bleeding, including occult bleeding .

Caution should be advised in patients receiving concomitant medication which may increase the risk of bleeding, such as anti-platelet agents (e.g. clopidogrel, ticlopidine) or selective serotonin reuptake inhibitors (SSRIs).

Headache or migraine-like headache which may occur especially at the beginning of ASASANTIN therapy should not be treated with analgesic doses of acetylsalicylic acid.

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 ASASANTIN Retard 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 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 after changes in dipyridamole dosage (see Interactions).

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.

Due to the acetylsalicylic acid component, ASASANTIN Retard should be used with caution in patients with asthma, allergic rhinitis, nasal polyps, chronic or recurring gastric or duodenal complaints, impaired renal or hepatic function or glucose-6-phosphate dehydrogenase deficiency.

In addition, caution is advised in patients hypersensitive to non-steroidal anti-inflammatory drugs (NSAIDs).

ASASANTIN Retard is not indicated for use in children and young people less than 16 years of age. There is a risk of Reye’s syndrome when children take acetylsalicylic acid.

The dose of acetylsalicylic acid in ASASANTIN Retard has not been studied in secondary prevention of myocardial infarction.

This product contains 106 mg of lactose and 22.64 mg sucrose per maximum recommended daily dose. Patients with rare hereditary problems of fructose intolerance and/or galactose intolerance e.g. galactosaemia should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

When dipyridamole is used in combination with acetylsalicylic acid or with warfarin, the statements regarding precautions, warnings and tolerance for these preparations must be observed.

Acetylsalicylic acid has been shown to enhance the effect of anticoagulants (e.g. coumarin derivatives and heparin), antiplatelet drugs (e.g clopidogrel, ticlopidine) valproic acid and phenytoin which may result in an increased risk of side effects. Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding. Gastrointestinal side effects also increase when acetylsalicylic acid is administered concomitantly with NSAIDs, corticosteroids, or chronic alcohol use. The 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 increases the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage should therefore be considered if use with dipyridamole is unavoidable.

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.

The effect of hypoglycaemic agents and the toxicity of methotrexate may be increased by the concomitant administration of acetylsalicylic acid.

Acetylsalicylic acid may decrease the natriuretic effect of spironolactone and inhibit the effect of uricosuric agents (e.g. probenecid, sulphinpyrazone).

The concomitant administration of ibuprofen but not certain other NSAIDs or paracetamol, in patients with increased cardiovascular risk may limit the beneficial cardiovascular effects of acetylsalicylic acid. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

4.6 Pregnancy and lactation

ASASANTIN Retard should only be used with caution in the first and second trimester if considered essential by the physician in terms of benefit and risk. ASASANTIN Retard should be avoided completely in the third trimester.

Dipyridamole and salicylates are excreted in breast milk. Therefore ASASANTIN Retard should not be administered.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Two large scale trials (ESPS-2, PRoFESS) enrolling a total of 26,934 patients, thereof 11,831 patients treated with ASASANTIN, were used to define the side effects profile of ASASANTIN. In addition, from spontaneous reporting also those events where facts and evidence qualified these as side effects have been included.

Due to the granularity of the coding system, bleeding events are distributed over several System Organ Classes (SOC); therefore, a summary description of **bleeding** is given in Table 1 below.

Table 1 Bleeding events broken down to any bleeding, major bleeding, haemorrhage intracranial and gastrointestinal haemorrhage

	ESPS-2		PRoFESS	
	ASASANTIN	Placebo	ASASANTIN	CLOPIDOGREL
Patients treated N (%)	1,650 (100)	1,649 (100)	10,055 (100)	10,040 (100)
Mean exposure (years)	1.4		1.9	2.1
Any Bleeding (%)	8.7	4.5	5.3	4.9
Major bleeding (%)	1.6	0.4	3.3	3.0
Haemorrhage intracranial (%)	0.6	0.4	1.2*	0.8*
Gastrointestinal haemorrhage (%)	4.3	2.6	1.9	1.6
* PRoFESS: DP/ASA intracranial haemorrhage (1.0%) and intraocular haemorrhage (0.2%) Clopidogrel intracranial haemorrhage (0.6 %) and intraocular haemorrhage (0.2 %)				

Side effects of ASASANTIN broken down to System Organ Classes:

Frequency: Very common > 1 in 10; Common > 1 in 100, < 1 in 10; Uncommon > 1 in 1,000, < 1 in 100; Rare > 1 in 10,000, < 1 in 1,000.

System Organ Class: MedDRA Term	Frequency
Blood and lymphatic system disorders:	
Anaemia	Common
Thrombocytopenia (reduction of platelet count)	Rare
Iron deficiency anaemia due to occult gastrointestinal bleeding	Rare
Immune system disorders:	Common
Hypersensitivity reactions rash urticaria severe bronchospasm angioedema	
Nervous system disorders:	
Haemorrhage intracranial	Common
Headache	Very Common
Migraine-like headache	Common
Dizziness	Very Common
Eye disorders:	
Eye haemorrhage (intraocular haemorrhage)	Uncommon
Cardiac disorders:	
Tachycardia	Uncommon
Worsening of symptoms of coronary heart disease (coronary artery disease)	Common
Syncope	Common
Vascular disorders:	
Hypotension	Uncommon
Hot flush	Uncommon
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common

Gastrointestinal disorders:	
Dyspepsia (epigastric distress)	Very Common
Vomiting	Common
Diarrhoea	Very Common
Nausea	Very Common
Gastritis erosive	Rare
Gastric ulcer, Duodenal ulcer	Uncommon
(severe) Gastrointestinal haemorrhage	Common
Abdominal pain	Very Common
Skin and subcutaneous tissue disorders:	
Skin haemorrhage	Not known*
contusion	
ecchymosis	
haematoma	
Musculoskeletal, connective tissue and bone disorders:	
Myalgia	Common
Investigations:	
Bleeding time prolonged	Not known*
Injury, poisoning and procedural complications:	
Post procedural haemorrhage	Not known*
Operative haemorrhage	Not known*

*These ADRs were not reported in clinical trials, therefore a frequency could not be calculated.

In addition to those side effects listed for ASASANTIN, for the relevant monocompounds also the below listed side effects are established; however, have not been reported for ASASANTIN yet.

Dipyridamole:
Additional side effects reported with dipyridamole monotherapy were as follows:
Dipyridamole has been shown to be incorporated into gallstones.

Acetylsalicylic acid:
Additional side effects reported with acetylsalicylic acid monotherapy were as follows;

Blood and lymphatic system disorders
Disseminated intravascular coagulation, coagulopathy

Immune system disorders
Anaphylactic reactions (especially in patients with asthma)

Metabolism and nutrition disorders
Hypoglycaemia (children), hyperglycaemia, thirst, dehydration, hyperkaleamia, metabolic acidosis, respiratory alkalosis

Psychiatric disorders
Confusional state

Nervous system disorders
Agitation, brain oedema, lethargy, convulsion

Ear and labyrinth disorders
Tinnitus, deafness

Cardiac disorders
Arrhythmia

Respiratory, thoracic and mediastinal disorders
Dyspnoea, gingival bleeding, laryngeal oedema, hyperventilation, pulmonary oedema, tachypnoea

Gastrointestinal disorders
Gastric ulcer perforation, duodenal ulcer perforation, melaena, haematemesis, pancreatitis

Hepatobiliary disorders
Hepatitis, Reye's syndrome

Skin and subcutaneous tissue disorders
Erythema exsudativum multiforme

Musculoskeletal, connective tissue and bone disorders
Rhabdomyolysis

Renal and urinary disorders
Renal failure, nephritis interstitial, renal papillary necrosis, proteinuria

Pregnancy, puerperium and perinatal conditions
Prolonged pregnancy, prolonged labour, small for dates baby, stillbirth, antepartum, haemorrhage, postpartum haemorrhage

General disorders and administration site conditions
Pyrexia, hypothermia

Investigations
Liver function test abnormal, blood uric acid increased (may lead to gout attacks), prothrombin time prolonged

4.9 Overdose

Symptoms

Because of the dose ratio of dipyridamole to acetylsalicylic acid, overdosage is likely to be dominated by signs and symptoms of dipyridamole overdose.

Due to the low number of observations, experience with dipyridamole overdose is limited.

Symptoms such as a warm feeling, flushes, sweating, accelerated pulse, restlessness, feeling of weakness, dizziness, drop in blood pressure and anginal complaints can be expected.

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms of salicylate overdose commonly include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features of salicylate poisoning include haematemesis, hyperpyrexia, hypogycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Therapy
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, diypridamole is not likely to be accessible to enhanced removal procedures. In the case of salicylate poisoning activated charcoal should be given to adults who present within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The antithrombotic action of the Acetylsalicylic acid (aspirin)/dipyridamole combination is based on the different biochemical mechanisms involved. Acetylsalicylic acid (aspirin) inactivates irreversibly the enzyme cyclo-oxygenase in platelets thus preventing the production of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction.

Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells in vitro and in vivo; the inhibition amounts to approximately 80% at maximum and occurs dose-dependently at therapeutic concentrations (0.5 – 2 mcg/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.

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 has also been shown in stroke patients to reduce the density of prothrombotic surface proteins (PAR-1: Thrombin receptor) on platelets as well as to reduce levels of c-reactive protein (CRP) and von Willebrand Factor (vWF). In-vitro investigations have shown that dipyridamole selectively inhibits inflammatory cytokines (MCP-1 and MMP-9) arising from platelet-monocyte interaction. Dipyridamole inhibits phosphodiesterase (PDE) in various tissues.

Whilst the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cGMP-PDE, thereby augmentin the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, identified as nitric oxide (NO)).

Dipyridamole increases the release of t-PA from microvascular endothelial cells and was shown to amplify the antithrombotic properties of endothelial cells on thrombus formation on adjacent subendothelial matrix in a dose dependent manner. Dipyridamole is a potent radical scavenger for oxy- and peroxy-radicals.

Dipyridamole also stimulates the biosynthesis and release of prostacyclin by the endothelium and reduces the thrombogenicity of subendothelial structures by increasing the concentration of the protective mediator 13-HODE (13-hydroxyoctadecadienic acid).

Whereas acetylsalicylic acid (aspirin) inhibits only platelet aggregation, dipyridamole in addition inhibits platelet activation and adhesion. Therefore an additional benefit from combining both drugs can be expected.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred.

However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Clinical Trials :

ASASANTIN Retard® was studied in a double-blind, placebo-controlled, 24-month study (**E**uropean **S**troke **P**revention **S**tudy **2**, **ESPS2**) in which 6602 patients had an ischemic stroke or transient ischemic attack (TIA) within three months prior to entry. Patients were randomized to one of four treatment groups: ASASANTIN Retard (ASA /extended-release dipyridamole) 25 mg/200 mg; extended-release dipyridamole (ER-DP) 200 mg alone; ASA 25 mg alone; or placebo. Patients received one capsule twice daily (morning and evening). Efficacy assessments included analyses of stroke (fatal or nonfatal) and death (from all causes) as confirmed by a blinded morbidity and mortality assessment group. In ESPS-2 ASASANTIN Retard reduced the risk of stroke by 22.1% compared to ASA. 50 mg/day alone (p =0.008) and reduced the risk of stroke by 24.4% compared to extended-release dipyridamole 400 mg/day alone (p = 0.002). ASASANTIN Retard reduced the risk of stroke by 36.8% compared to placebo (p <0.001). The results of the ESPS-2 study are supported by the **E**uropean/Australasian **S**troke **P**revention in **R**eversible **I**schaemia **T**rial **(ESPRIT)** study which studied a combination treatment of diypridamole 400 mg daily (83% of patients treated with the extended-release dipyridamole formulation) and ASA 30-325 mg daily. A total of 2739 patients after ischaemic stroke of arterial origin were enrolled in the ASA-alone (n = 1376) and combination ASA plus dipyridamole (n = 1363) arm. The primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction (MI), or major bleeding complications. Patients in the ASA plus dipyridamole group showed a 20% risk reduction (p<0.05) for the primary composite endpoint compared with those in the ASA alone group (12.7% vs. 15.7%; hazard ratio [HR] 0.80, 95% CI 0.66–0.98).

The PRoFESS (**PR**eventi**o**n Regimen **F**or **E**ffectively avoiding **S**econd **S**trokes) study was a randomized, parallel group, international, double-blind, double-dummy, active and placebo controlled, 2x2 factorial study to compare ASASANTIN with clopidogrel, and telmisartan with matching placebo in the prevention of stroke in patients who had already experienced an ischaemic stroke of noncardioembolic origin. Individuals who were ≥ 55 years of age and who had had an ischemic stroke within 90 days of entry to the study were included. A total of 20,332 patients were randomized to ASASANTIN (n= 10,181) or clopidogrel (n = 10,151), both given on a background of standard treatment. The primary endpoint was the time to first recurrent stroke of any type.
The incidence of the primary endpoint was similar in both treatment groups (9.0% for ASASANTIN vs. 8.8% for clopidogrel; HR 1.01, 95 % CI 0.92-1.11). No significant difference between the ASASANTIN and clopidogrel treatment groups were detected for several other important pre-specified endpoints, including the composite of recurrent stroke, myocardial infarction, or death due to vascular causes (13.1% in both treatment groups; HR 0.99, 95 % CI 0.92-1.07) and the composite of recurrent stroke or major haemorrhagic event (11.7% for ASASANTIN vs. 11.4% for clopidogrel; HR 1.03, 95 % CI 0.95-1.11). The functional neurological outcome 3 months post recurrent stroke was assessed by the Modified Rankin Scale (MRS) and no significant difference in the distribution of the MRS between ASASANTIN and clopidogrel was observed (p = 0.3073 by Cochran-Armitage test for linear trend).

5.2 Pharmacokinetic properties

There is no noteworthy pharmacokinetic interaction between the extended release pellets of dipyridamole and aetylsalicylic acid (aspirin). Therefore pharmacokinetics of ASASANTIN Retard is reflected by the pharmacokinetics of the individual components.

Dipyridamole

(Most pharmacokinetic data refer to healthy volunteers.)

With dipyridamole, there is dose linearity for all doses used in therapy.

For long-term treatment dipyridamole modified release capsules, formulated as pellets were developed. The pH dependent solubility of dipyridamole which prevents dissolution in the lower parts of the gastro-intestinal tract (where sustained release preparations must still release the active principle) was overcome by combination with tartaric acid. Retardation is achieved by a diffusion membrane, which is sprayed onto the pellets.

Various kinetic studies at steady state showed, that all pharmacokinetic parameters 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.

Absorption
The absolute bioavailability is about 70%. As first pass removes approx. 1/3 of the dose administered, near to complete absorption of dipyridamole following administration of acetylsalicylic acid (aspirin) modified release capsules can be assumed.

Peak plasma concentrations of dipyridamole following a daily dose of 400 mg acetylsalicylic acid (aspirin) (given as 200 mg b.i.d) are reached about 2-3 hours after administration. There is no relevant effect of food on the pharmaconkinetics of dipyridamole in acetylsalicylic acid (aspirin) modified release capsules.

Distribution
The apparent volume of distribution of the central compartment (Vc) is about 5 l (similar to plasma volume). The apparent volume of distribution at steady state is about 100 l, reflecting distribution to various compartments.

The drug does not cross the blood-brain barrier to a significant extent. The 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 primarily 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 present as parent compound, and 20% of the total amount as monoglucuronide. The pharmacodynamic activity of dipyridamole glucuronides is considerably lower than of dipyridamole.

Elimination
The dominant half-life with oral administration is about 40 minutes as it is the case with i.v. administration.

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 approximately 250 ml/min and mean residence time is about 11 hours (resulting from an intrinsic MRT of about 6.4 hr and a mean time of absorption of 4.6 h).

As with i.v. administration a prolonged terminal elimination half-life of approximately 13 hours 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 b.i.d. regimens of modified release capsules. There is no significant accumulation of the drug with repeated dosing.

Kinetics in elderly
Dipyridamole plasma concentrations (determined as AUC) in elderly subjects (> 65 years) were about 50% higher for tablet treatment and about 30% higher with intake of ASASANTIN Retard modified release capsules than in young (< 55 years) subjects. The difference is caused mainly by reduced clearance; absorption appears to be similar.

Similar increases in plasma concentrations in elderly patients were observed in the ESPS2 study for PERSANTIN® modified release capsules as well as for ASASANTIN Retard.

Kinetics in patients with renal impairment
Since renal excretion is very low (5%), no change in pharmaconkinetics 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 >100mL/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite if data were corrected for differences in age.

Kinetics in patients with hepatic impairment
Patients with hepatic insufficiency show no change in plasma concentrations of dipyridamole, but an increase of (pharmacodynamically low active) glucuronides. It is suggested to dose dipyridamole without restriction as long as there is no clinical evidence of liver failure.

Acetylsalicylic acid (aspirin)

Absorption
After oral administration acetylsalicylic acid (aspirin) is rapidly and completely absorbed in the stomach and intestine. Approximately 30% of the dose of acetylsalicylic acid (aspirin) is hydrolyzed presystemically to salicylic acid. Maximum plasma concentrations after a daily dose of 50 mg acetylsalicylic acid from ASASANTIN Retard (given as 25 mg twice daily) are attained after 30 minutes of each dose, and peak plasma concentration at steady state amounted to approximately 360 ng/mL for acetylsalicylic acid (aspirin); maximum plasma concentrations of salicylic acid are achieved after 60-90 minutes and amount to approximately 1100 ng/ml. There is no relevant effect of food on the pharmacodynamics of acetylsalicylic acid in ASASANTIN Retard.

Distribution
Acetylsalicylic acid (aspirin) is rapidly converted to salicylate but is the predominant form of the drug in the plasma during the first 20 minutes following oral administration. Plasma acetylsalicylic acid (aspirin) concentrations decline rapidly with a half-life of approx. 15 minutes. Its major metabolite, salicylic acid, is highly bound to plasma proteins, and its binding is concentration-dependent (nonlinear). At low concentrations (<100 µg/mL), approximately 90% of salicylic acid is bound to albumin. Salicylates which are widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and fetal tissues.

Metabolism
Acetylsalicylic acid (aspirin) is metabolised rapidly by non-specific esterases to salicylic acid. Salicylic acid is metabolised to salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, and to a minor extent to gentisic acid and gentisuric acid. The formation of the major metabolites salicyluric acid and salicylic phenolic glucuronide is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes.

Elimination
Acetylsalicylic acid (aspirin) has an elimination half-life of elimination of 15-20 minutes in plasma; the major metabolite salicylic acid has a half-life of elimination of 2-3 hours at low doses (e.g. 325 mg), which may rise to 30 hours at higher doses because of non-linearity in metabolism and plasma protein binding.

More than 90% of acetylsalicylic acid (aspirin) is excreted as metabolites via the kidneys. The fraction of salicylic acid excreted unchanged in the urine increases with increasing dose and the renal clearance of total salicylate also increases with increasing urinary pH.

Kinetics in patients with renal impairment
Renal dysfunction: acetylsalicylic acid (aspirin) is to be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/min). An increase in total plasma concentrations and in the unbound fraction of salicylic acid has been reported.

Kinetics in patients with hepatic impairment
Hepatic dysfunction: acetylsalicylic acid is to be avoided in patients with severe hepatic insufficiency. An increase in the unbound fraction of salicylic acid has been reported.

5.3 Preclinical safety data

Dipyridamole and acetylsalicylic acid have 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
Povidone (K25)
Methacrylic acid-methyl methacrylate copolymer (1:2)
Talc
Acacia
Hypromellose Phthalate
Hypromellose
Triacetin
Dimeticone 350
Stearic acid 50
Lactose Monohydrate
Aluminium Stearate
Colloidal Anhydrous silica
Maize Starch
Microcrystalline cellulose
Sucrose
Titanium Dioxide (E171)

Capsule shells:
Gelatin
Red and yellow iron oxides (E172)
Titanium Dioxide (E171)

Printing Ink:
Shellac
Ethanol
Isopropyl alcohol
Propylene glycol
N-butyl alcohol
Ammonium Hydroxide
Potassium hydroxide
Purified water
Red Iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the container and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C
Discard any capsules remaining 6 weeks after opening.

6.5 Nature and contents of container

Overlabelled cardboard outer containing bottle.
Pack size: 60 capsules

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 Parallel Product Authorisation Holder

Imbat Limited
Unit L2, North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/128/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th November 2009

10 DATE OF REVISION OF THE TEXT