SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dipyridamol/Acetylsalicylzuur Sandoz 200/25 mg, capsules met gereguleerde afgifte, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg of dipyridamole and 25 mg of acetylsalicylic acid.

Excipients with known effect
Each capsule contains 29.2 mg of lactose, 0.872 mg of methyl parahydroxybenzoate (E 218), 0.218 mg of propyl parahydroxybenzoate (E 216), 0.04 mg of soya lecithin (E 322), 0.0029 mg of azo colouring agent ponceau 4R (E 124) and 0.0264 mg of azo colouring agent sunset yellow (E 110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release capsule, hard.

Capsule containing acetylsalicylic acid in standard release form and dipyridamole in modified-release form.

Capsule with orange coloured cap and white to off-white coloured body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary prevention of ischaemic stroke and transient ischaemic attacks.

4.2 Posology and method of administration

Posology
Adults, including the elderly
The recommended dose is one capsule twice daily, usually one in the morning and one in the evening.

Paediatric population
[Nationally completed name] is not indicated for use in children due to safety concerns (see section 4.4)

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 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.

Renal impairment

Due to the acetylsalicylic acid component, [Nationally completed name] is contraindicated in patients with severe renal impairment (see section 4.3). Caution should be exercised in patients with mild or moderate renal impairment (see section 4.4).

Hepatic impairment
Due to the acetylsalicylic acid component, [Nationally completed name] is contraindicated in patients with severe hepatic impairment (see section 4.3). Caution should be exercised in patients with mild or moderate hepatic impairment (see section 4.4).

Method of administration
Oral use.

The capsules should be swallowed whole without chewing together with a glass of water, preferably with meals.

[Nationally completed name] capsules should not be taken at the same time as an alcoholic beverage (see section 4.5).

4.3 Contraindications

- Hypersensitivity to the active substances, any salicylate or to any of the excipients listed in section 6.1
- Peanut or soya allergies
- History of haemorrhagic cerebrovascular accident
- Gastric symptoms or patients who have experienced gastric pain when previously using this medicine
- Active peptic ulcer and/or gastrointestinal bleeding (see section 4.4)
- Severe hepatic or renal insufficiency
- Haemorrhagic diathesis or coagulation disorders such as haemophilia and hypoprothrombinaemia
- Methotrexate used at doses > 15 mg/week (see section 4.5)

4.4 Special warnings and precautions for use

Bleeding disorders
Due to the risk of bleeding, as with other antiplatelet agents, [Nationally completed name] 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 medicinal products which may increase the risk of bleeding, such as anti-platelet agents (e.g. clopidogrel, ticlopidine), anticoagulants,selective serotonin reuptake inhibitors (SSRIs), or anagrelide (see section 4.5).

Headache or migraine-like headache
Headache or migraine-like headache which may occur especially at the beginning of [Nationally completed name] therapy should not be treated with analgesic doses of acetylsalicylic acid (see section 4.2).

Cardiovascular disorders
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).

The dose of acetylsalicylic acid in [Nationally completed name] has not been studied in secondary prevention of myocardial infarction.

Stress testing with intravenous dipyridamole
Patients treated with regular oral doses of [Nationally completed name] 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 medicinal products containing oral dipyridamole twenty-four hours prior to being treated with intravenous dipyridamole.

Myasthenia gravis
In patients with myasthenia gravis readjustment of therapy may be necessary after changes in dipyridamole dose (see section 4.5).

Biliary 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.

Acetylsalicylic acid related warnings
Due to the acetylsalicylic acid component, [Nationally completed name] 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 (contraindicated if severe, see section 4.3), or glucose-6-phosphate dehydrogenase deficiency.

Hypersensitivity
In addition, caution is advised in patients hypersensitive to other non-steroidal anti-inflammatory drugs.

Children and adolescents
[Nationally completed name] is not indicated for use in children and young people. There is a possible association between acetylsalicylic acid and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason acetylsalicylic acid should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

Prior to surgical procedures, e.g. tooth extraction, where there is an increased risk of bleeding, discontinuation of treatment with [Nationally completed name] should be considered. Typically, treatment should be discontinued 7 days before surgery.

[Nationally completed name] contains lactose, parahydroxybenzoates, azo colouring agents and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains the azo colouring agents ponceau 4R (E 124) and sunset yellow (E 110), which may cause allergic reactions.

This medicinal product contains methyl parahydroxybenzoate (E 218) and propyl parahydroxybenzoate (E 216), which may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1 mmol (23 mg) sodium per modified -release hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products affecting coagulation
When dipyridamole is used in combination with other substances impacting coagulation such as anticoagulants and antiplatelet agents, the safety profile for these medicinal products must be observed.

Acetylsalicylic acid has been shown to enhance the effect of anticoagulants (e.g. coumarin derivatives and heparin), antiplatelets (e.g. clopidogrel, ticlopidine), selective serotonin reuptake inhibitors (SSRIs), or anagrelide and may increase the risk of bleeding. 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.

Anticonvulsants
Acetylsalicylic acid may enhance the effect of valproic acid and phenytoin with possible increased risk of side effects.

NSAIDs/ Corticosteroids/ Alcohol
Gastrointestinal side effects may increase when acetylsalicylic acid is administered concomitantly with NSAIDs, corticosteroids or chronic alcohol use.

There is some experimental evidence that ibuprofen interferes with acetylsalicylic acid induced inhibition of platelet cyclo-oxygenase. This interaction could reduce the beneficial cardiovascular effects of acetylsalicylic acid, however the evidence for this is not conclusive. Further, in view of the known increased risk of gastrointestinal toxicity associated with NSAID and acetylsalicylic acid co-medication, this combination should be avoided wherever possible. When such a combination is necessary the balance of gastrointestinal and cardiovascular risks should be considered.

Adenosine
Dipyridamole increases the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dose should therefore be considered if use with dipyridamole is unavoidable.

Antihypertensives
Dipyridamole may increase the hypotensive effect of blood pressure lowering medicinal products.

Cholinesterase inhibitors
Dipyridamole counteracts the anticholinesterase effect of cholinesterase inhibitors thereby potentially aggravating myasthenia gravis.

Hypoglycaemics/ Methotrexate
The effect of hypoglycaemic agents and the toxicity of methotrexate may be increased by the concomitant administration of acetylsalicylic acid. Concomitant use with methotrexate > 15 mg/week is contraindicated (see section 4.3). For lower doses weekly blood count tests should be carried out during the first weeks of treatment. Enhanced monitoring is recommended in the presence of impaired renal function, as well as in the elderly.

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

Metamizole
Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose acetylsalicylic acid for cardioprotection.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of dipyridamole and acetylsalicylic acid in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

From the beginning of the sixth month of pregnancy, all prostaglandin synthesis inhibitors including acetylsalicylic acid may expose:

- the foetus to
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
  - renal dysfunction, which may progress to renal failure with oligo-hydroamniosis
  - inhibition of the trombocyte function
- the mother and the neonate at the end of pregnancy, to
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

This is reversible on withdrawal of treatment.

Intake of acetylsalicylic acid within 5 days of estimated parturition gives an increased tendency to bleeding in the mother and the foetus/newborn.

[Nationally completed name] is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
Dipyridamole and salicylates are excreted in breast milk. Adverse effects on the suckling child cannot be excluded. Therefore, a decision should be made whether to discontinue breast-feeding or to discontinue/abstain from [Nationally completed name] therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on human fertility with the combination product dipyridamole/acetylsalicylic acid..

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be advised that symptoms such as dizziness and confusional state have been reported in clinical trials. If patients experience such symptoms, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Two large scale trials (ESPS-2, PRoFESS) enrolling a total of 26,934 patients, thereof 11,831 patients treated with dipyridamole/acetylsalicylic acid, were used to define the side effects profile of

dipyridamole/acetylsalicylic acid. These data are supplemented with the extensive dipyridamole/ acetylsalicylic acid post-marketing experience.

The most frequently reported adverse reactions are headache, dizziness and gastrointestinal events such as dyspepsia, diarrhoea, nausea and abdominal pain. Most important serious adverse reactions associated with dipyridamole/ acetylsalicylic acid were bleeding events.

Table of side effects
The following adverse reactions have been reported in ESPS-2 and PRoFESS and from spontaneous reporting.
Frequency: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Very common	Common	Uncommon	Rare	Frequency not known*
Blood and lymphatic system disorders		Anaemia		Thrombocyto-penia, iron deficiency anaemia due to occult gastrointestinal bleeding	Disseminated intravascular coagulation[2], coagulopathy [2]
Immune system disorders		Hypersensitivity reactions (including rash, urticaria, severe bronchospasm, angioedema)			Anaphylactic reactions (especially in patients with asthma)[2]
Metabolism and nutrition disorders					Hypoglycae mia (children)[2], hyperglycae mia[2], thirst[2], dehydration[2], hyperkalaemi a[2], metabolic acidosis[2], respiratory alkalosis[2]
Psychiatric disorders					Confusional state[2]
Nervous system disorders	Headache, dizziness	Haemorrhage intracranial, migraine-like headache (especially at the beginning of treatment)			Agitation[2], brain oedema[2], lethargy[2], convulsion[2]

System Organ Class	Very common	Common	Uncommon	Rare	Frequency not known*
Eye disorders			Eye haemorrhage		
Ear and labyrinth disorders					Tinnitus[2], deafness[2]
Cardiac disorders		Worsening of symptoms of coronary artery disease, syncope	Tachycardia		Arrhythmia[2]
Vascular disorders			Hypotension, hot flush		
Respiratory, thoracic and mediastinal disorders		Epistaxis			Dyspnoea[2], gingival bleeding[2], laryngeal oedema[2], hyperventilation[2], pulmonary oedema[2], tachypnoea[2]
Gastrointestinal disorders	Nausea, diarrhoea, dyspepsia, abdominal pain	Vomiting, gastrointestinal haemorrhage	Gastric ulcer, duodenal ulcer	Gastritis erosive	Gastric ulcer perforation[2], duodenal ulcer perforation[2], melaena[2], haematemesis[2], pancreatitis[2]
Hepatobiliary disorders					Dipyridamole has been shown to be incorporated into gallstones[1], hepatitis[2], Reye's syndrome[2]
Skin and subcutaneous tissue disorders					Skin haemorrhage (including contusion, ecchymosis, haematoma), erythema exsudativum multiforme[2]

System Organ Class	Very common	Common	Uncommon	Rare	Frequency not known*
Musculoskeletal and connective tissue disorders		Myalgia			Rhabdomyolysis[2]
Renal and urinary disorders					Renal failure[2], nephritis interstitial[2], renal papillary necrosis[2], proteinuria[2]
Pregnancy, puerperium and perinatal conditions					Prolonged pregnancy[2], prolonged labour[2], small for dates baby[2], stillbirth[2], haemorrhage in pregnancy[2], postpartum haemorrhage[2]
General disorders and administration site conditions					Pyrexia[2], hypothermia[2]
Investigations					Bleeding time prolonged, liver function test abnormal[2], blood uric acid increased (may lead to gout attacks)[2], prothrombin time prolonged[2]
Injury, poisoning and procedural complications					Post procedural haemorrhage, procedural haemorrhage

[1]Identified adverse reactions of dipyridamole monotherapy
[2]Identified adverse reactions of acetylsalicylic acid monotherapy
*These ADRs were not reported in clinical trials, therefore a frequency could not be calculated.

Description of selected side effects
The most important serious adverse reactions associated with dipyridamole/ acetylsalicylic acid were bleeding events. Data from ESPS-2 and PRoFESS trials for bleeding events including major bleeding were evaluated. Bleeding events categorized as any bleeding, major bleeding, intracranial bleeding and gastrointestinal bleeding:

In the controlled ESPS-2 trial, 1650 patients were treated in the dipyridamole/acetylsalicylic acid group (100%) and 1649 in the placebo group (100%). The mean duration of treatment was 1.4 years. The overall incidence of bleeding was 8.7% in the dipyridamole/acetylsalicylic acid group and 4.5% in the placebo group. The incidence of major bleeding was 1.6% and 0.4% respectively. The incidence of intracranial bleeding was 0.6% and 0.4% respectively, whilst the incidence of gastrointestinal bleeding was 4.3% and 2.6% respectively.

In the PRoFESS trial, a total of 10,055 patients were treated in the dipyridamole/acetylsalicylic acid group (100%). The mean duration of treatment was 1.9 years. The overall incidence of bleeding was 5.3%. The incidence of major bleeding was 3.3%. The incidence of intracranial bleeding was 1.2% (including intraocular bleeding (0.2%)), whilst the incidence of gastrointestinal bleeding was 1.9%.

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 national reporting system listed in Appendix V of the QRD template; to be completed nationally}

4.9 Overdose

Symptoms
Because of the dose ratio of dipyridamole to acetylsalicylic acid, overdose 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, and anginal complaints can be expected. A drop in blood pressure and tachycardia might be observed.

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, hypoglycaemia, 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.

Dizziness and tinnitus can be symptoms of overdose, particularly in elderly patients.

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, dipyridamole 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

Pharmacotherapeutic group: Antithrombotic agents; Platelet aggregation inhibitors excl. heparin, combinations, ATC code: B01AC30.

Mechanism of action
The antithrombotic action of the acetylsalicylic acid/dipyridamole combination is based on the different biochemical mechanisms involved. Acetylsalicylic acid 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.

Thus, platelet aggregation in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (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 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 augmenting 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 peroxyradicals.

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).

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

Clinical efficacy and safety
Dipyridamole/acetylsalicylic acid 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: 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 dipyridamole/acetylsalicylic acid 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 ($p = 0.002$). Dipyridamole/acetylsalicylic acid 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**event**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 dipyridamole/acetylsalicylic acid with clopidogrel, and telmisartan with matching placebo in the prevention of stroke in patients who had previously experienced an ischaemic stroke of noncardioembolic origin. A total of 20,332 patients were randomized to dipyridamole/acetylsalicylic acid (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 dipyridamole/acetylsalicylic acid vs. 8.8% for clopidogrel; HR 1.01, 95 % CI 0.92-1.11). No significant difference between the dipyridamole/acetylsalicylic acid 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 dipyridamole/acetylsalicylic acid 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 dipyridamole/acetylsalicylic acid and clopidogrel was observed (p = 0.3073 by Cochran-Armitage test for linear trend).

More patients randomised to ASA+ER-DP (4.1%) than to clopidogrel (3.6%) experienced a major haemorrhagic event (HR = 1.15; 95% CI 1.00, 1.32; p = 0.0571). The difference between the treatment groups was mainly due to the higher incidence of non-life threatening major haemorrhagic events in the ASA+ER-DP group (2.9%) than in the clopidogrel group (2.5%) while the incidences of life threatening haemorrhagic events were similar in both groups (128 patients vs. 116 patients). The overall incidence of intracranial haemorrhage was higher in the ASA+ER-DP group (1.4%) than in the clopidogrel group (1.0%) resulting in a HR of 1.42 (95% CI 1.11, 1.83) with a p-value of 0.0062. The difference between the treatment groups resulted mainly from the higher incidence of haemorrhagic strokes in the ASA+ER-DP group (0.9% vs. clopidogrel 0.5%).

5.2 Pharmacokinetic properties

There is no noteworthy pharmacokinetic interaction between the extended release pellets of dipyridamole and acetylsalicylic acid. Therefore pharmacokinetics of [Nationally completed name] 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 gastrointestinal 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 modified release capsules can be assumed.

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

Distribution
Owing to its high lipophilicity, log P 3.92 (n-octanol/0.1n, NaOH), dipyridamole distributes to many organs.

In animals, dipyridamole is distributed preferentially to the liver, then to the lungs, kidneys, spleen and heart. Although, the preferred distribution of dipyridamole has not been established in humans, its major presence in human liver, kidney and heart after oral administration has been extensively reported.

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.

In virtue of the presence of BCPR, an active drug uptake transporter in the human placenta, dipyridamole could be transferred into the foetal direction.

Biotransformation
Metabolism of dipyridamole occurs in the liver. Dipyridamole is metabolized 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 h 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.

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 dipyridamole/acetylsalicylic acid 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 older people were observed in the ESPS2 study for dipyridamole modified release capsules as well as for dipyridamole/acetylsalicylic acid.

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.

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
Absorption
After oral administration acetylsalicylic acid is rapidly and completely absorbed in the stomach and intestine. Approximately 30% of the dose of acetylsalicylic acid is hydrolyzed presystemically to salicylic acid. Maximum plasma concentrations after a daily dose of 50 mg acetylsalicylic acid from dipyridamole/acetylsalicylic acid (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; 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 [Nationally completed name].

Distribution
Acetylsalicylic acid 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 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 are widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

Biotransformation
Acetylsalicylic acid 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 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 nonlinearity in metabolism and plasma protein binding.

More than 90% of acetylsalicylic acid 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.

Renal impairment
Renal dysfunction: acetylsalicylic acid 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.

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 separately have been extensively investigated in animal models and no clinically significant findings have been observed at doses equivalent to therapeutic doses in humans. In rat studies, foetotoxic and teratogenic effects were observed with acetylsalicylic acid at high maternotoxic doses. Toxicokinetic evaluations were not included in these studies.

Studies with the drug combination dipyridamole/acetylsalicylic acid in a ratio of 1:4 revealed additive, but no potentiating toxic effects. A single dose study in rats using dipyridamole/acetylsalicylic acid in a ratio of 1:0.125 gave comparable results to studies with the 1:4 combination.

Fertility studies were only performed with the individual components. No impairment of fertility was observed with dipyridamole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dipyridamole pellets:
Tartaric acid
Hypromellose
Acacia
Talc
Povidone
Methacrylic acid-methyl methacrylate copolymer (1:2)
Hypromellose phthalate
Dimethicone 350
Triacetin
Stearic acid

Acetylsalicylic acid tablet:
Cellulose, microcrystalline
Lactose anhydrous
Maize starch pregelatinised
Silica, colloidal anhydrous
Stearic acid
Polyvinyl alcohol – part hydrolysed
Titanium dioxide (E 171)
Talc
Quinoline yellow aluminium lake (E 104)
Lecithin, soya (E 322)
Xanthan gum (E 415)

Capsule shells:
Gelatin
Purifed water
Methyl parahydroxybenzoate (E 218)
Propyl parahydroxybenzoate (E 216)
Ponceau 4R (E 124) (contains sodium)
Patent blue V (E 131) (contains sodium)

Quinoline yellow (E 104) (contains sodium)
Sunset yellow (E 110) (contains sodium)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Shelf life after first opening of the bottle:
30 days

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
Keep the bottle tightly closed.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

White, HDPE bottles with child resistant closure, containing a desiccant made from molecular sieves.

Pack sizes of 30, 30 (sample), 50, 60 (2x30), 100 (2x50).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 109873

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 19 september 2012
Datum van laatste verlenging: 15 augustus 2017

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 7: 8 februari 2024