Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
Aggrenox®

Active substances: Dipyridamole, acetylsalicylic acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains dipyridamole 200 mg and acetylsalicylic acid (ASA) 25 mg.

Contains lactose monohydrate and sucrose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Controlled-release capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Secondary prevention of ischaemic strokes and transient ischaemic attacks - TIA.

4.2 Posology and method of administration
The recommended dose is one capsule twice daily, usually one in the morning and one in the evening.

The capsules should be swallowed whole with liquid and can be taken with or after meals.

Aggrenox is intended for long-term treatment; the duration of treatment will be determined by the physician.

Aggrenox is not recommended for use in children owing to insufficient experience in this population (see also Section 4.4).

Alternative regimen in the event of intolerable headaches
In the event of intolerable headaches during treatment initiation, patients can be switched 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
- Known hypersensitivity to salicylates or to any of the ingredients of Aggrenox
- Rare hereditary conditions resulting in intolerance to any of the excipients (see section 4.4: Special warnings and precautions for use)

Because of its ASA component, Aggrenox is contraindicated in patients with active gastric or duodenal ulcers, patients with bleeding disorders and patients in the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Owing to the risk of bleeding, Aggrenox, in common other antiplatelet agents, should be used with caution in patients at increased bleeding risk. Patients should be monitored carefully for any signs of bleeding, including occult bleeding.

Caution is required in patients receiving concomitant medication which may increase the risk of bleeding, such as antiplatelet agents (e.g. clopidogrel, ticlopidine or ASA) or selective serotonin reuptake inhibitors (SSRIs).

Headache or migraine-like headache, which may occur especially at the beginning of Aggrenox therapy, must not be treated with analgesic doses of ASA.

Owing to the vasodilator properties of dipyridamole, Aggrenox should be used with caution in patients with severe coronary heart disease (including unstable angina or recent myocardial infarction), left ventricular outflow obstruction or haemodynamic instability (e.g. decompensated heart failure).

Aggrenox should be discontinued 24 h prior to stress testing for coronary heart disease with intravenous dipyridamole. Clinical experience shows that failure to do so may impair the sensitivity of the test.

During treatment with Aggrenox, readjustment of therapy may be necessary in patients with myasthenia gravis (see section 4.5: Interaction with other medicinal products and other forms of interaction).

In a small number of patients, 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 suspected ascending cholangitis and had been treated with dipyridamole for a number of years. There is no evidence that dipyridamole was the initiating factor in causing gallstones to form in these patients. Bacterial deglucuronidation of conjugated dipyridamole in bile may be the mechanism responsible for the presence of dipyridamole in gallstones.

Because of its ASA component, Aggrenox should be used with caution in patients with asthma, allergic rhinitis, nasal polyps, chronic or recurring gastric or duodenal complaints, renal or hepatic impairment, glucose-6-phosphate dehydrogenase deficiency, other allergies (such as those involving skin reactions, urticaria and pruritus) or chronic respiratory diseases.

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

Patients receiving concomitant therapy with anticoagulants such as coumarin derivatives and heparin (although not low-dose heparin) require particularly careful medical supervision.

The dose of ASA in Aggrenox has not been investigated in clinical trials on the secondary prevention of myocardial infarction.

It should be borne in mind that Aggrenox may prolong bleeding time if taken prior to surgical procedures (including minor procedures such as dental extraction).

There is a possible association between ASA and Reye's syndrome in children. Because of the risk of Reye's syndrome, Aggrenox is contraindicated in children or adolescents with febrile diseases or viral infections (with or without fever). Reye's syndrome is a very rare disease which affects the brain and liver and can be fatal.

Aggrenox contains 53 mg lactose and 11.3 mg sucrose per capsule (equivalent to 106 mg lactose and 22.6 mg sucrose per maximum recommended daily dose). Patients with rare hereditary galactose or fructose intolerance, lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Aggrenox.

4.5 Interaction with other medicinal products and other forms of interaction

Dipyridamole may:

- increase the plasma levels and therefore the cardiovascular effects of adenosine (this may necessitate adjustment of the adenosine dose);
- abolish the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis;
- increase the blood pressure-lowering effect of antihypertensives.

If dipyridamole is used concomitantly with medications affecting coagulation, such as anticoagulants and antiplatelet agents, the safety profile of these medications must be monitored.

When dipyridamole was administered in combination with warfarin (a coumarin derivative), bleeding was no greater in frequency or severity than when warfarin was administered alone.

The ASA component of Aggrenox can increase the effect of the following, leading to an increased risk of undesirable effects:

- anticoagulants such as coumarin derivatives and heparin
- antiplatelet agents such as clopidogrel, ticlopidine and ASA
- antidiabetic agents such as sulphonylureas (blood glucose levels may fall)
- methotrexate (toxicity may be increased)
- valproic acid and phenytoin
- SSRIs (increased risk of bleeding)
- systemic corticosteroids, with the exception of hydrocortisone as replacement therapy in Addison's disease, or alcohol (increased risk of gastrointestinal ulcers and gastrointestinal bleeding)
- NSAIDs, corticosteroids and chronic alcohol use (increased risk of undesirable gastrointestinal effects)
- digoxin (increased plasma levels).

Dipyridamole may decrease the effects of:

- aldosterone antagonists (spironolactone and canrenoate)
- loop diuretics such as furosemide
- antihypertensives, particularly ACE inhibitors
- uricosuric agents such as probenecid or sulphinpyrazone.

The desired cardiovascular effects of ASA may be decreased by ibuprofen (though not by other NSAIDs or paracetamol).

Combining dipyridamole with ASA does not increase the bleeding risk.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of dipyridamole and low-dose ASA in pregnant women. Preclinical studies revealed no hazard potential.

Pregnancy

Aggrenox should only be used in the first and second trimesters if the benefit is thought to outweigh the risk; it is contraindicated in the third trimester.

Lactation

Salicylates and dipyridamole are excreted in small quantities in breast milk. Therefore, Aggrenox should only be administered to breast-feeding mothers if the benefit is thought to outweigh the risk.

Fertility

No studies have been performed on the effect of Aggrenox on fertility in humans (see section 5.3).

4.7 Effects on ability to drive and use machines

In studies carried out in groups of 24 subjects, Aggrenox had no effect on safety-related performance compared with placebo. In particular, no sedative effects or interactions with alcohol were observed. There is therefore no evidence that, when used in accordance with the prescribing instructions, Aggrenox will affect the ability to drive, use machines or carry out other potentially hazardous tasks.

However, patients should be advised that symptoms such as dizziness and confusional state have been reported in clinical trials. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience such symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Two large-scale clinical trials (ESPS-2, PRoFESS) enrolling a total of 26,934 patients, of whom 11,831 were allocated to Aggrenox, were used to define the adverse event profile. Events from spontaneous reports were also taken into account where sufficient data were available to warrant their classification as an adverse event.

Owing to the granularity of the coding system, bleeding events are distributed over several system organ classes. A summary description of bleeding events is therefore given below.

Bleeding events categorised as any bleeding, major bleeding, intracranial bleeding and gastrointestinal bleeding:

In the ESPS-2 trial, 1650 patients were treated in the Aggrenox 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 Aggrenox 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 Aggrenox 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%.

The undesirable effects of Aggrenox are listed below according to system organ class and frequency. The following frequency convention has been used for the classification of undesirable effects:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10,000 to < 1/1000
Very rare	< 1/10,000
Not known	Frequency cannot be estimated from the available data

Blood and lymphatic system disorders

Common:	Anaemia
Rare:	Thrombocytopenia, iron deficiency anaemia due to occult gastrointestinal bleeding

Immune system disorders

Common:	Hypersensitivity reactions such as rash and urticaria, severe bronchospasm and angioedema

Nervous system disorders

Very common:	Headache*, dizziness*
Common:	Intracranial bleeding, migraine-like headache* (particularly at the start of treatment)

Eye disorders

Uncommon:	Eye haemorrhage

Cardiac disorders	
Common:	Worsening of symptoms of coronary heart disease (PRoFESS: 0.07%; ESPS-2: 7.6% (Aggrenox) / 7.8% (placebo)), syncope (PRoFESS: 1.5% within 7 days of the start of treatment, uncommon thereafter; ESPS-2: 1.0% (Aggrenox) / 0.5% (placebo))
Uncommon:	Tachycardia
Vascular disorders	
Uncommon:	Hot flushes, hypotension
Respiratory, thoracic and mediastinal disorders	
Common:	Epistaxis
Gastrointestinal disorders	
Very common:	Dyspepsia, abdominal pain, nausea*, diarrhoea*
Common	Vomiting*, (severe) gastrointestinal bleeding
Uncommon:	Gastric ulcers, duodenal ulcers
Rare:	Erosive gastritis
Skin and subcutaneous tissue disorders	
Frequency not known:	Skin haemorrhages such as haematomas or ecchymoses
Musculoskeletal, connective tissue and bone disorders	
Common:	Myalgia*
Investigations	
Frequency not known:	Prolonged bleeding time
Injury, poisoning and procedural complications	
Frequency not known:	Increased postoperative or other postprocedural bleeding, increased intraoperative bleeding

* Usually resolves with continued therapy

The individual components of Aggrenox are known to cause the following undesirable effects in addition to those listed above for the combination product:

Additional undesirable effects with dipyridamole alone were:

Incorporation of dipyridamole into gallstones (see section 4.4)

Additional undesirable effects with ASA alone were:

Blood and lymphatic system disorders
Disseminated intravascular coagulation, coagulopathy

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

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

Psychiatric disorders
Confusion

Nervous system disorders
Agitation, cerebral 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

Vascular disorders
Shock (mainly in patients with asthma)

Gastrointestinal disorders
Gastric ulcer perforation, duodenal ulcer perforation, melaena, haematemesis, pancreatitis, micro-haemorrhages

Hepatobiliary disorders
Hepatitis, Reye's syndrome

Skin and subcutaneous tissue disorders
Severe skin reactions, including erythema exsudativum multiforme

Musculoskeletal, connective tissue and bone disorders
Rhabdomyolysis

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

Pregnancy, puerperium and perinatal conditions
Prolonged pregnancy, prolonged labour, small-for-gestational age neonate, stillbirth, antepartum haemorrhage, postpartum haemorrhage

General disorders and administration site conditions
Pyrexia, hypothermia

Investigations
Abnormal liver function test, increased blood uric acid level (potentially leading to gout attacks), prolonged prothrombin time

There have been rare to very rare reports of major bleeding events such as cerebral haemorrhage (especially in patients who had uncontrolled high blood pressure and/or who were receiving concomitant treatment with anticoagulants); in isolated cases, these events may be life-threatening

4.9 Overdose

Symptoms of overdose

Acute overdoses will probably lead initially to dipyridamole-induced cardiovascular symptoms, followed by dose-dependent symptoms of ASA intoxication.

Dipyridamole
A feeling of warmth, facial flushing, sweating, accelerated pulse, restlessness, feelings of weakness and dizziness, a fall in blood pressure and anginal symptoms may occur.
ASA
A distinction is made between chronic intoxication ("salicylism"), in which CNS symptoms such as light-headedness, dizziness or nausea predominate, and acute intoxication.
The most prominent feature of acute intoxication is a severe disturbance of acid-base balance. Respiratory alkalosis due to hyperpnoea occurs even at therapeutic doses. It is compensated by increased renal excretion of bicarbonate, which normalises blood pH. After toxic doses, compensation becomes insufficient and blood pH and bicarbonate concentrations fall. Plasma PCO_2 may be temporarily nor-

mal, suggesting metabolic acidosis, whereas a combination of respiratory and metabolic acidosis is in fact present.

Symptoms of acute intoxication
Symptoms of mild acute intoxication (associated with plasma levels of 200 - 400 µg/ml): Hyperventilation, tinnitus, nausea, vomiting, impaired vision and hearing, headache, dizziness and confusional states may occur in addition to disturbances of acid-base balance or electrolyte balance (e.g. potassium loss).

Symptoms of severe intoxication (associated with plasma levels of 400 µg/ml) may include delirium, tremor, dyspnoea, sweating, dehydration, hyperthermia and coma. In cases of fatal intoxication, death normally results from respiratory failure.

Treatment of overdose

Dipyridamole
Gastric emptying should be considered. Administration of xanthine derivatives such as aminophylline may abolish the haemodynamic effect of dipyridamole.
Owing to its wide distribution in tissues and its predominantly hepatic elimination, dipyridamole is not likely to be accessible to enhanced removal procedures.

ASA
Treatment of ASA intoxication is guided by the extent, stage and clinical symptoms of the intoxication. It encompasses the usual measures for reducing absorption of ASA, monitoring and correcting water and electrolyte balance and restoring normal temperature regulation and respiration.

Treatment consists chiefly of measures to accelerate excretion and to restore the acid-base and electrolyte balance. Diuretics are given in addition to infusions of sodium bicarbonate and potassium chloride. The urine should be alkalinised in order to increase salicylate ionisation and thus reduce salicylate reabsorption into the renal tubules.
It is highly advisable to monitor blood parameters such as pH, PCO_2, bicarbonate and potassium. In severe cases, haemodialysis may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Combination of platelet aggregation inhibitors

ATC codes:
1. B01AC07
2. B01AC06

Dipyridamole
Dipyridamole inhibits the uptake of adenosine into erythrocytes, platelets and endothelial cells *in vitro* and *in vivo*. This inhibition, which is dose-dependent at therapeutic concentrations (0.5 - 2 µg/ml) and which reaches a maximum of about 80%, leads to increased local extracellular concentrations of adenosine acting on the platelet A_2 receptor. The adenosine stimulates platelet adenylate cyclase and increases platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels, thereby inhibiting platelet aggregation induced by various stimuli such as platelet-activating factor (PAF), collagen and adenosine diphosphate (ADP). The decreased platelet aggregation reduces platelet consumption to normal levels. Adenosine also has a vasodilator effect and this is one of the mechanisms by which dipyridamole produces vasodilation.

In stroke patients, dipyridamole has also been shown to decrease the density of prothrombotic surface proteins (PAR-1 thrombin receptor) on platelets and reduce blood levels of C-reactive protein (CRP) and von Willebrand factor (vWF). *In-vitro* studies have shown that dipyridamole selectively inhibits gene expression of the inflammatory cytokine MCP-1 (monocyte chemoattractant protein-1) and release of the plaque-destabilising enzyme MMP-9 (matrix metalloproteinase-9), both of which factors arise from platelet-monocyte interaction.

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. cAMP-PDE is only weakly inhibited but, at therapeutic concentrations of dipyridamole, cyclic-3',5'-guanosine monophosphate-PDE (cGMP-PDE) is inhibited to a marked degree. The reduced breakdown of cGMP that this entails leads to an increase in platelet cGMP via the enhanced stimulatory action of endothelium-derived relaxing factor (EDRF), which has been identified as nitric oxide.

Dipyridamole increases the release of tissue plasminogen activator (t-PA) from microvascular endothelial cells and dose-dependently enhances the antithrombotic properties of endothelial cells on thrombus formation on adjacent subendothelial matrix. Dipyridamole is a potent radical scavenger for oxy and peroxy radicals.

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-hydroxyoctadecadienoic acid).

ASA
ASA inhibits collagen-induced platelet aggregation by the irreversible acetylation of the enzyme complex cyclooxygenase (COX). This enzyme is also found in platelets and endothelial cells and produces the precursors (endoperoxides) for prostaglandin and thromboxane biosynthesis. In endothelial cells, the main product of the endoperoxides is prostacyclin, a powerful vasodilator and inhibitor of platelet aggregation. Platelets, on the other hand, form large quantities of thromboxane A_2, which induces aggregation and has a vasoconstrictor effect. The (indirect) inhibition of thromboxane formation by ASA is therefore the cause of the inhibition of collagen-induced platelet aggregation which has been detected *in vitro* and *ex vivo*. The inhibition of cyclooxygenase in endothelial cells is not permanent, unlike in platelets, since new enzyme is formed as a result of protein biosynthesis. However, in the anuclear platelets, which have a survival time of 8 - 10 days, virtually no protein synthesis takes place and the enzyme remains inhibited for the whole of the platelet's life. This is the reason for the cumulative inhibitory effect on platelet aggregation achieved by repeated doses of ASA

Combination of dipyridamole and ASA
The *in-vitro* and *ex-vivo* biochemical and pharmacological studies described confirm that dipyridamole has antithrombotic effects which are independent of the inhibition of thromboxane formation by ASA. Since the formation of a thrombus involves the close interaction of a number of different prothrombotic stimuli, it is rational to combine two molecules with different antithrombotic mechanisms of action (which dipyridamole and ASA have been shown to have) in order to achieve greater antithrombotic efficacy.

Clinical efficacy

Aggrenox was studied in a double-blind, placebo-controlled, 24-month trial (**E**uropean **S**troke **P**revention **S**tudy **2**; ESPS-2) carried out in 6602 patients who had had an ischaemic stroke or transient ischaemic attack within three months prior to entry. Patients were randomised to one of four treatment groups: Aggrenox (ASA 25 mg and prolonged-release dipyridamole 200 mg), prolonged-release dipyridamole 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 non-fatal) and death (from all causes) as confirmed by a blinded morbidity and mortality assessment group. In ESPS-2, Aggrenox reduced the risk of stroke by 23.1% compared to ASA 50 mg/day ($p = 0.006$), by 24.7% compared to prolonged-release dipyridamole 400 mg/day ($p = 0.002$) and by 37.0% compared to placebo ($p < 0.001$).

The results of the ESPS-2 trial are supported by the **E**uropean/Australasian **S**troke **P**revention in **R**eversible **I**schaemia **T**rial (ESPRIT), which studied a combination of dipyridamole 400 mg/day (with 83% of patients receiving the prolonged-release form of dipyridamole and 8% receiving Aggrenox) and ASA 30 - 325 mg/day. A total of 2739 patients who had had an ischaemic stroke of arterial origin were treated, with 1376 allocated to ASA alone and 1362 to ASA plus dipyridamole. The primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myo-

cardial infarction 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 to those in the ASA group (13% vs. 16%; hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.66 - 0.98).

The PRoFESS (**PR**eventi**o**n Regimen **F**or **E**ffectively avoiding **S**econd **S**trokes) trial was an international randomised, parallel-group, double-blind, double-dummy, 2x2 factorial trial comparing Aggrenox with clopidogrel, and telmisartan with matching placebo, in the prevention of stroke in patients who had previously experienced an ischaemic stroke of non-cardioembolic origin. A total of 20,332 patients were randomised to Aggrenox (n = 10,181) or clopidogrel (n = 10,151), which were both given on a background of standard treatment. The primary endpoint was the time to first recurrence of stroke of any type.

The incidence of the primary endpoint was similar in the two treatment groups (9.0% for Aggrenox vs. 8.8% for clopidogrel; HR 1.01, 95% CI 0.92 - 1.11). No significant differences between the Aggrenox and clopidogrel 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 Aggrenox vs. 11.4% for clopidogrel; HR 1.03, 95% CI 0.95 - 1.11). The functional neurological outcome three months post-recurrent stroke was assessed by the modified Rankin Scale (mRS); no significant difference in the distribution of the mRS score between Aggrenox and clopidogrel was observed ($p = 0.3073$ by Cochran-Armitage test for linear trend).

5.2 Pharmacokinetic properties

There is no relevant pharmacokinetic interaction between the dipyridamole in the prolonged-release pellets and the ASA. The pharmacokinetics of Aggrenox can therefore be described in terms of the pharmacokinetics of the individual components.

Dipyridamole

Most of the pharmacokinetic data refer to healthy volunteers.

The pharmacokinetics of dipyridamole have been shown to be dose-linear for all doses used therapeutically.

For long-term treatment, capsules containing prolonged-release dipyridamole pellets were developed. The solubility of dipyridamole shows a pH dependence which prevents the drug from dissolving in the lower gastrointestinal tract. As prolonged-release preparations depend on continued drug absorption in the higher pH environment of the lower gastrointestinal tract, the dipyridamole was combined with tartaric acid. Prolonged release of the dipyridamole is achieved with the aid of a diffusion membrane which is sprayed onto the pellets.

Various pharmacokinetic studies at steady state showed that all parameters which are suitable for characterising the pharmacokinetic properties of prolonged-release preparations are equivalent or somewhat improved following prolonged-release dipyridamole twice daily compared to immediate-release dipyridamole tablets three or four times daily; bioavailability is slightly higher, peak plasma levels are similar, trough plasma levels are considerably higher and the peak-trough difference is smaller.

Absorption

Absolute bioavailability is about 70%. As about a third of the dose is removed by first-pass metabolism, it can be assumed that dipyridamole is almost completely absorbed following administration of Aggrenox.

After a daily dose of 400 mg dipyridamole in the form of Aggrenox (200 mg twice daily), peak plasma levels are reached about 2 - 3 hours following administration. The mean peak plasma level at steady state is 1.98 µg/ml (1.01 - 3.99 µg/ml) and the mean trough level at steady state is 0.53 µg/ml (0.18 - 1.01 µg/ml). Food intake has no relevant effect on the pharmacokinetics of the prolonged-release dipyridamole in Aggrenox.

Distribution
Dipyridamole is highly lipophilic (log P = 3.92 (n-octanol/0.1N NaOH)) and is therefore distributed to many organs.
In animals, dipyridamole is distributed preferentially to the liver, then to the lungs, kidneys, spleen and heart. The rapid distribution phase observed following intravenous administration is not seen following oral administration.
The apparent volume of distribution of the central compartment (V_c) is about 5 litres (similar to plasma volume). The apparent volume of distribution at steady state (V_{ss}), reflecting distribution to various compartments, is about 100 litres.

Dipyridamole does not cross the blood-brain barrier to any appreciable extent.

Dipyridamole crosses the placenta only in very small quantities. In one woman studied, the concentration of dipyridamole in breast milk was found to be 1/17th of the plasma concentration.

Binding of dipyridamole to proteins is about 97 - 99%. The substance is primarily bound to α_1-acid glycoprotein and albumin.

Metabolism
Dipyridamole is metabolised in the liver. Metabolism occurs by conjugation with glucuronic acid, primarily to monoglucuronide and, to a small extent, to diglucuronide. In plasma, about 80% of the total amount is present as the parent compound and 20% as monoglucuronide. The pharmacodynamic activity of dipyridamole glucuronides is considerably weaker than that of dipyridamole.

Elimination
The dominant half-life following oral administration, as with intravenous administration, is about 40 min.
Renal excretion of parent compound is negligible (< 0.5%) and urinary excretion of the glucuronide metabolite is low (5%). The metabolites are mostly (about 95%) excreted via bile into the faeces, with some evidence of enterohepatic recirculation.
Total clearance is approximately 250 ml/min and mean residence time (MRT) is about 11 h, resulting from an intrinsic MRT of 6.4 h and a mean absorption time of 4.6 h. A prolonged terminal half-life of about 13 h is observed after both intravenous and oral administration. This terminal half-life represents only a small proportion of the total area under the plasma concentration-time curve (AUC) and is thus of relatively minor importance, as emphasised by the fact that steady state is achieved in two days at a dosage of two prolonged-release capsules daily. Repeated administration of Aggrenox does not lead to any significant accumulation.

Kinetics in the elderly
Plasma dipyridamole concentrations, determined as AUC, in elderly patients (> 65 years) were about 50% higher following administration of tablets and about 30% higher following administration of Aggrenox than in young patients (< 55 years). The difference is caused mainly by lower clearance; absorption appears to be comparable. In elderly patients in the ESPS-2 trial, similar increases in plasma concentrations were observed for Aggrenox and dipyridamole tablets 200 mg.

Kinetics in patients with renal impairment
Since renal excretion of dipyridamole is very low (5%), no change in pharmacokinetics is anticipated in patients with renal failure. In ESPS-2 patients, with creatinine clearances ranging from 15 ml/min to > 100 ml/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolites when data were corrected for differences in age.

Kinetics in patients with hepatic impairment
In patients with liver failure, there is no change in the plasma levels of dipyridamole although levels of the glucuronides, which have weak pharmacodynamic activity, are increased. It is therefore recommended that dipyridamole be given at its normal dosage unless there is clinical evidence of liver failure.

<u>ASA</u>

Absorption
Following oral administration, ASA is rapidly and completely absorbed in the stomach and intestine. Approximately 30% of the dose is presystemically hydrolysed to salicylic acid. After a daily dose of 50 mg ASA in the form of Aggrenox (25 mg twice daily), peak plasma levels are reached 30 min after administration. Steady-state peak plasma levels of ASA after two 25-mg doses daily were 360 ng/ml. Peak plasma levels of salicylic acid (about 1100 ng/ml) are attained within 60 - 90 min. Food intake has no relevant effect on the pharmacodynamic activity of the ASA component of Aggrenox.

Distribution
ASA is rapidly converted to salicylate but remains the predominant form of the substance in plasma in the first 20 min after oral administration. Plasma levels of ASA decline rapidly with a half-life of about 15 min. The major metabolite of ASA, salicylic acid, is highly bound to plasma proteins; its binding is concentration-dependent (non-linear). At low concentrations (< 100 µg/ml), approximately 90% of salicylic acid is bound to albumin. Salicylates are widely distributed to all tissues and body fluids, including the central nervous system, breast milk and foetal tissues.

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

Elimination
ASA has an elimination half-life from plasma of 15 - 20 min. At low doses (e.g. 325 mg), the major metabolite salicylic acid has an elimination half-life of 2 - 3 h; at high doses, this may rise to 30 h because of non-linearity in metabolism and plasma protein binding.
More than 90% of ASA is excreted as metabolites via the kidneys. The fraction of salicylic acid excreted unchanged in the urine increases with increasing dose. The renal clearance of salicylate also increases with increasing urinary pH.

Kinetics in patients with renal impairment
ASA is contraindicated in patients with severe renal failure (glomerular filtration rate < 10 ml/ min). An increase in total plasma levels and in the unbound fraction of salicylic acid has been reported.

Kinetics in patients with hepatic impairment
ASA is contraindicated in patients with severe liver failure. An increase in the unbound fraction of salicylic acid has been reported.

5.3 Preclinical safety data
Acute toxicity
The acute toxicity of the combination after a single oral dose was low and was due entirely to the ASA component. The dipyridamole did not contribute to toxicity at any of the dipyridamole:ASA ratios tested (1:0.125 or 1:4 to 1:6). No organ changes were observed; the cause of death was cardiovascular failure.

Repeated-dose toxicity
Repeated-dose toxicity studies on the combination were carried out in rats and dogs over periods of up to 6 months at doses of up to 400 mg/kg. The dipyridamole:ASA ratios tested were 1:4 to 1:5.
There were no particular signs of toxicity in rats at the doses tested. In dogs, doses of 200 mg/kg and above caused gastrointestinal changes (due to the ASA content of 320 mg/kg) and myocardial/endocardial changes and nephritis (due to the dipyridamole content of 40 mg/kg). The same changes were observed when the components were given individually at comparable doses. This demonstrates that combining the individual components does not lead to any additive or potentiating toxic effects.

Toxicity to reproduction

Embryotoxicity studies were carried out in rats and rabbits using maternotoxic doses of the combination in which the dipyridamole:ASA ratio was 1:5. An ASA-only group given an ASA dose equivalent to that used in the high-dose combination group was used as a positive control.
The maternotoxicity of the high doses of the combination (405 mg/kg in rats, 135 mg/kg in rabbits) led to increased resorption rates (up to 100% in rats) and reduced litter weights. Malformations were observed only in the ASA and high-dose combination groups; the ASA dose used in both of these groups was extremely high (110 mg/kg).

Fertility studies and studies on peri- and postnatal development have only been carried out on the individual components. No impairment of fertility was observed.
Because of the known effects of ASA in the later stages of pregnancy, the combination of dipyridamole and ASA is recommended only if the expected benefit is thought to outweigh the risk. The combination is contraindicated in the last three months of pregnancy

Mutagenicity
In-vitro and *in-vivo* studies revealed no evidence of mutagenic potential.

Carcinogenicity
Studies in rats and mice at doses of up to 450 mg/kg (corresponding to a dipyridamole dose of 75 mg/kg and an ASA dose of 375 mg/kg) did not reveal any evidence of tumorigenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate, cellulose microcrystalline, maize starch dried, silica colloidal anhydrous, aluminium stearate, sucrose, talc, acacia, tartaric acid, polyvidone (K 25), Eudragit S100 (methacrylic acid-methyl meth-acrylate copolymer (1:2)) , hypromellose, hypromellose phthalate, glycerol triacetate, dimeticone 350, stearic acid, hard gelatin capsule size 0, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), water.
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6.2 Incompatibilities
None known

6.3 Special precautions for storage
Store below 25˚C
Keep the bottle tightly closed in the original package.
After first opening of the bottle, the capsules should be used within one month.

6.4 Nature and contents of containers
Nature of containers:
White polypropylene wide-neck bottle with child-resistant screw cap containing a desiccant made from 90% silica gel and 10% molecular sieve
Pack sizes:
Sample pack containing 20 capsules
Original pack containing 60 capsules
Not all pack sizes may be marketed.

7. MARKETING AUTHORISATION

Manufacturer: Boehringer Ingelheim GmbH, Germany
Registration holder: Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301
Registration number: 140 53 31735

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved on March 2014.