SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Molita 200 mg/25 mg modified-release capsules, hard

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

Excipients: Each capsule contains 29.2 mg lactose anhydrous, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), soya lecithin (E322), ponceau 4R (E124) and sunset yellow (E110).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Modified-release capsule, hard.

Capsule containing acetylsalicylic acid (aspirin) 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
For oral administration.

Adults, including the elderly
The recommended dose is one capsule twice daily, usually one in the morning and one in the evening.
The capsules should be swallowed whole without chewing together with a glass of water.

**Paediatric population**
Molita is not recommended for use in children due to insufficient data on safety, efficacy and posology.

**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 (aspirin) 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, Molita 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, Molita 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).

**Alcohol**
Molita capsules should not be taken at the same time as an alcoholic beverage (see section 4.5).

### 4.3 Contraindications
- Hypersensitivity to any component of the product or salicylates
- 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
- Glucose-6-phosphatedehydrogenase deficiency (G6Pd deficiency)
- Methotrexate used at doses > 15 mg/week (see section 4.5)

### 4.4 Special warnings and precautions for use
Due to the risk of bleeding, as with other antiplatelet agents, Molita 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), please see section 4.5.

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

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 Molita 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.

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 (aspirin) component, Molita 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).

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

Molita is not indicated for use in children and young people. There is a possible association between acetylsalicylic acid (aspirin) 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 (aspirin) should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

The dose of acetylsalicylic acid (aspirin) in Molita has not been studied in secondary prevention of myocardial infarction.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Molita capsules contain ponceau 4R (E124) and sunset yellow (E110) colouring agents, which may cause allergic reactions.

Molita capsules also contain methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Gastrointestinal side effects may increase when acetylsalicylic acid (aspirin) is administered concomitantly with NSAIDs, corticosteroids or chronic alcohol use. The addition of dipyridamole to acetylsalicylic acid (aspirin) does not increase the incidence of bleeding events. When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.

Dipyridamole 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 (aspirin). 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 elderly.

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

There is some experimental evidence that ibuprofen interferes with acetylsalicylic acid (aspirin) induced inhibition of platelet cyclo-oxygenase. This interaction could reduce the beneficial cardiovascular effects of acetylsalicylic acid (aspirin), 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 (aspirin) 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.

Molita capsules should not be taken at the same time as alcohol, as alcohol may increase the rate of release of dipyridamole from the modified-release preparation.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of dipyridamole and acetylsalicylic acid (aspirin) 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 (aspirin) 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 oligohydroamniosis
  - 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 (aspirin) within 5 days of estimated parturition gives an increased tendency to bleeding in the mother and the foetus/newborn.

Molita is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation
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 Molita therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Fertility studies and studies covering the peri-postnatal period have not been performed with the combination.
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 dipyridamole/acetylsalicylic acid (aspirin), were used to
define the side effects profile of dipyridamole/acetylsalicylic acid (aspirin). 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

<table>
<thead>
<tr>
<th></th>
<th>ESPS-2</th>
<th>PRoFESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated (N</td>
<td>1,650 (100)</td>
<td>1,649 (100)</td>
</tr>
<tr>
<td>(%))</td>
<td></td>
<td>10,055 (100)</td>
</tr>
<tr>
<td>Mean exposure (years)</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Any bleeding (%)</td>
<td>8.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial (%)</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage (%)</td>
<td>4.3</td>
<td>2.6</td>
</tr>
</tbody>
</table>

* PRoFESS: intracranial haemorrhage (1.0%) and intraocular haemorrhage (0.2%)

Side effects of dipyridamole/acetylsalicylic acid (aspirin) broken down to System
Organ Classes:

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); and Very rare (< 1/10,000)
including isolated reports.

System Organ Class:

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders:</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Thrombocytopenia (reduction of platelet count)</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Iron deficiency anaemia due to occult gastrointestinal bleeding</td>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

**Immune system disorders:**
- Hypersensitivity reactions
  - rash
  - urticaria
  - severe bronchospasm
  - angioedema
  - Common

**Nervous system disorders:**
- Haemorrhage intracranial
- Headache
- Migraine-like headache
- Dizziness
  - Common
  - Very Common
  - Common
  - Very Common

**Eye disorders:**
- Eye haemorrhage (intraocular haemorrhage)
  - Uncommon

**Cardiac disorders:**
- Tachycardia
- Worsening of symptoms of coronary heart disease (coronary artery disease)
- Syncope
  - Uncommon
  - Common
  - Common

**Vascular disorders:**
- Hypotension
- Hot flush
  - Uncommon
  - Uncommon

**Respiratory, thoracic and mediastinal disorders:**
- Epistaxis
  - Common

**Gastrointestinal disorders:**
- Dyspepsia (epigastric distress)
- Vomiting
- Diarrhoea
- Nausea
- Gastritis erosive
- Gastric ulcer, Duodenal ulcer
- (severe) Gastrointestinal haemorrhage
- Abdominal pain
  - Very Common
  - Common
  - Very Common
  - Rare
  - Uncommon
  - Common
  - Very Common

**Skin and subcutaneous tissue disorders:**
- Skin haemorrhage
  - contusion
  - ecchymosis
  - haematoma
  - Not known*

**Musculoskeletal, connective tissue and bone disorders:**
- Myalgia
  - Common

**Investigations:**
- Bleeding time prolonged
  - Not known*
In addition to those side effects listed for dipyridamole/acetylsalicylic acid (aspirin), for the relevant monocompounds also the below listed side effects are established; however, have not been reported for dipyridamole/acetylsalicylic acid (aspirin) yet.

**Dipyridamole:**
Additional side effects reported with dipyridamole monotherapy were as follows:

- Dipyridamole has been shown to be incorporated into gallstones (See "Special warnings and precautions for use").

**Acetylsalicylic acid (aspirin):**
Additional side effects reported with acetylsalicylic acid (aspirin) 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, hyperkalaemia, 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 (aspirin), 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, 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, particularly in elderly patients, be symptoms of overdose.

**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.

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 A2-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).

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.

Clinical Trials:
Dipyridamole/acetylsalicylic acid (aspirin) was studied in a double-blind, placebo-controlled, 24-month study (European Stroke Prevention Study 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 (fetal or nonfetal) and death (from all causes) as confirmed by a blinded morbidity and mortality assessment group. In ESPS-2 dipyridamole/acetylsalicylic acid (aspirin) 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 (aspirin) 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 European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) study [112] which studied a combination treatment of dipyridamole 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 (PRevention Regimen For Effectively avoiding Second Strokes) study was a randomized, parallel group, international, double-blind, double-dummy, active and placebo controlled, 2x2 factorial study to compare dipyridamole/acyetylsalicylic acid (aspirin) 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/acyetylsalicylic acid (aspirin) (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/acyetylsalicylic acid (aspirin) vs. 8.8% for clopidogrel; HR 1.01, 95% CI 0.92-1.11). No significant difference between the dipyridamole/acyetylsalicylic acid (aspirin) 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/acyetylsalicylic acid (aspirin) 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/acyetylsalicylic acid (aspirin) 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 (aspirin). Therefore pharmacokinetics of Molita 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 (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 pharmacokinetics of dipyridamole in acetylsalicylic acid (aspirin) 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.

**Metabolism**

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.

**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 dipyridamole/acetylsalicylic acid (aspirin) 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 dipyridamole modified release capsules as well as for dipyridamole/acetylsalicylic acid (aspirin).

**Kinetics in patients with 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.

**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 (aspirin) from dipyridamole/acetylsalicylic acid (aspirin) (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 (aspirin) in Molita.

**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 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 nonlinearity 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 (aspirin) 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 (aspirin) 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 (aspirin) at high maternotoxic doses. Toxicokinetic evaluations were not included in these studies.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Acetylsalicylic acid (aspirin) tablet:
Cellulose, microcrystalline
Lactose anhydrous
Corn starch, pre-gelatinised
Silica, colloidal anhydrous
Stearic acid
Polyvinyl alcohol – part hydrolysed
Titanium dioxide (E171)
Talc
Quinoline yellow aluminium lake (E104)
Lecithin, soya (E322)
Xanthan gum (E415)

Capsule shells:
Gelatin
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Ponceau 4R (E124)
Patent blue V (E131)
Quinoline yellow (E104)
Sunset yellow (E110)
Titanium dioxide (E171)

6.2 Incompatibilities

None stated.
6.3 Shelf life
2 years
Discard any capsules remaining 30 days after first opening the bottle.

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 precautions.

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

7 MARKETING AUTHORITY
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HU17 0LD
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
   PL 08553/0466

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   09/10/2012

10 DATE OF REVISION OF THE TEXT
    11/02/2013