ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Plavix 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate).
Excipients: each tablet contains 3 mg lactose and 3.3 mg hydrogenated castor oil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, round, biconvex, engraved with «75» on one side and «1171» on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopidogrel is indicated in adults for the prevention of atherothrombotic events in:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

- Patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

For further information please refer to section 5.1.

4.2 Posology and method of administration

- Adults and elderly

  Clopidogrel should be given as a single daily dose of 75 mg with or without food.

  In patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300-mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1).
  - ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300-mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early

as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section 5.1).

- Paediatric patients
  The safety and efficacy of clopidogrel in children and adolescents have not yet been established.

- Renal impairment
  Therapeutic experience is limited in patients with renal impairment (see section 4.4).

- Hepatic impairment
  Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 Special warnings and precautions for use

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8). As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs including Cox-2 inhibitors. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.5).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients (see section 4.2).

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.2).

Plavix contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.4).

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

Acetylsalicylic acid (ASA): ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).

Heparin: in a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

Thrombolytics: the safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.4).

Other concomitant therapy: a number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital, cimetidine, or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P_{450} 2C9. This could potentially lead to increased plasma levels of medicinal products such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by Cytochrome P_{450} 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Plavix.

4.7 Effects on ability to drive and use machines

Clopidogrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies are discussed below. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment.

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for ASA.

In CURE, the major bleeding event rate for clopidogrel+ASA was dose-dependent on ASA (<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo+ASA (<100mg: 2.0%; 100-200mg: 2.3%; >200mg: 4.0%). The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months (clopidogrel: 9.6%; placebo: 6.6%), 1-3 months (clopidogrel: 4.5%; placebo: 2.3%), 3-6 months (clopidogrel: 3.8%; placebo: 1.6%), 6-9 months (clopidogrel: 3.2%; placebo: 1.5%), 9-12 months (clopidogrel: 1.9%; placebo: 1.0%). There was no excess in major bleeds with clopidogrel + ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel+ASA vs. 5.3% placebo+ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel+ASA, and 6.3% for placebo+ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel + ASA group (17.4%) vs. the placebo + ASA group (12.9%).The incidence of major bleeding was similar between groups (1.3% versus 1.1% for the clopidogrel + ASA and the placebo + ASA groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups (0.6% versus 0.5% in the clopidogrel + ASA and the placebo + ASA groups, respectively).

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: 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). Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis

System Organ Class	Common	Uncommon	Rare	Very rare
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

4.9 Overdose

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.
No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC-04.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the

amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

The safety and efficacy of clopidogrel have been evaluated in 4 double-blind studies involving over 80,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75 mg/day or ASA 325 mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p = 0.045), which corresponds, for every 1,000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at p = 0.003) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR = 7.3%; CI: -5.7 to 18.7 [p=0.258]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR = -4.0%; CI: -22.5 to 11.7 [p=0.639]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤75 years.

Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

Acute coronary syndrome

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, N=6,259) or placebo (N=6,303), both given in combination with ASA (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel and placebo was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

The use of clopidogrel in CURE was associated with a decrease in the need of thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel-treated group and 1,187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the clopidogrel-treated group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel treated group and 363 (5.8%) in the placebo treated group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering medicinal products, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily).

In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1,752) or placebo (n=1,739), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients ≥ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint, representing an absolute reduction of 6.7% and a 36 % odds reduction in favor of clopidogrel (95% CI: 24, 47%; p < 0.001), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day, n=22,961) or placebo (n=22,891), in combination with ASA (162 mg/day), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients ≥ 60 years (26% ≥ 70 years) and 54.5% patients who received fibrinolytics.

Clopidogrel significantly reduced the relative risk of death from any cause by 7% (p = 0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

5.2 Pharmacokinetic properties

After repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/l) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative, which represents about 85% of the circulating compound in plasma. Peak plasma levels of this metabolite (approx. 3mg/l after repeated 75 mg oral doses) occurred approximately 1 hour after dosing.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by Cytochrome P_{450} isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

The kinetics of the main circulating metabolite were linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94% respectively). The binding is non-saturable *in vitro* over a wide concentration range.

Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 ml/min) and to levels observed in other studies with healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

The pharmacokinetics and pharmacodynamics of clopidogrel were assessed in a single and multiple dose study in both healthy subjects and those with cirrhosis (Child-Pugh class A or B). Daily dosing for 10 days with clopidogrel 75 mg/day was safe and well tolerated. Clopidogrel C_{max} for both single dose and steady state for cirrhotics was many fold higher than in normal subjects. However, plasma levels of the main circulating metabolite together with the effect of clopidogrel on ADP-induced platelet aggregation and bleeding time were comparable between these groups.

5.3 Preclinical safety data

During non clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.
At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Mannitol (E421)
Macrogol 6000
Microcrystalline cellulose
Hydrogenated castor oil
Low substituted hydroxypropylcellulose

Coating:
Hypromellose (E464)
Lactose
Triacetin (E1518)
Titanium dioxide (E171)
Red iron oxide (E172)
Carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

In PVC/PVDC/aluminium blisters, store below 30°C.
In all aluminium blisters, this medicinal product does not require any special storage conditions.

6.5 Nature and content of container

PVC/PVDC/Aluminium blisters or all aluminium blisters in cardboard cartons containing 7, 14, 28, 30, 84, 90 and 100 film-coated tablets.

PVC/PVDC/Aluminium or all aluminium perforated unit-dose blister packs in cardboard cartons containing 50x1 film-coated tablets.

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 AUTHORISATION HOLDER

Sanofi Pharma Bristol-Myers Squibb SNC
174 Avenue de France
F-75013 Paris – France

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/069/001a - Cartons of 28 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/001b - Cartons of 28 film-coated tablets in all aluminium blisters
EU/1/98/069/002a - Cartons of 50x1 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/002b - Cartons of 50x1 film-coated tablets in all aluminium blisters
EU/1/98/069/003a - Cartons of 84 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/003b - Cartons of 84 film-coated tablets in all aluminium blisters
EU/1/98/069/004a - Cartons of 100 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/004b - Cartons of 100 film-coated tablets in all aluminium blisters
EU/1/98/069/005a - Cartons of 30 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/005b - Cartons of 30 film-coated tablets in all aluminium blisters
EU/1/98/069/006a - Cartons of 90 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/006b - Cartons of 90 film-coated tablets in all aluminium blisters
EU/1/98/069/007a - Cartons of 14 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/007b - Cartons of 14 film-coated tablets in all aluminium blisters
EU/1/98/069/011a - Cartons of 7 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/98/069/011b - Cartons of 7 film-coated tablets in all aluminium blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 July 1998
Date of latest renewal: 15 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA): http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Plavix 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of clopidogrel (as hydrogen sulphate).
Excipients: each tablet contains 12 mg lactose and 13.2 mg hydrogenated castor oil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, oblong, engraved with «300» on one side and «1332» on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopidogrel is indicated in adults for the prevention of atherothrombotic events in:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

- Patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

For further information please refer to section 5.1.

4.2 Posology and method of administration

- Adults and elderly

  This 300 mg tablet of clopidogrel is intended for use as a loading dose in patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1).
  - ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300-mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age clopidogrel, should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the

combination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section 5.1).

For the maintenance dose, clopidogrel should be given as a single daily dose of 75 mg with or without food. For this dose, tablets containing 75 mg are available.

- Paediatric patients
  The safety and efficacy of clopidogrel in children and adolescents have not yet been established.

- Renal impairment
  Therapeutic experience is limited in patients with renal impairment (see section 4.4).

- Hepatic impairment
  Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 Special warnings and precautions for use

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8). As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors, or non-steroidal anti-inflammatory drugs including Cox-2 inhibitors. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.5).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients (see section 4.2).

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.2).

Plavix contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.4).

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

Acetylsalicylic acid (ASA): ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).

Heparin: in a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

Thrombolytics: the safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.4).

Other concomitant therapy: a number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital, cimetidine, or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P_{450} 2C9. This could potentially lead to increased plasma levels of medicinal products such as phenytoin and tolbutamide and the NSAIDs, which are

metabolised by Cytochrome P_{450} 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Plavix.

4.7 Effects on ability to drive and use machines

Clopidogrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies are discussed below. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment.

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for ASA.

In CURE, the major bleeding event rate for clopidogrel+ASA was dose-dependent on ASA (<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo+ASA (<100mg: 2.0%; 100-200mg: 2.3%; >200mg: 4.0%). The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months (clopidogrel: 9.6%; placebo: 6.6%), 1-3 months (clopidogrel: 4.5%; placebo: 2.3%), 3-6 months (clopidogrel: 3.8%; placebo: 1.6%), 6-9 months (clopidogrel: 3.2%; placebo: 1.5%), 9-12 months (clopidogrel: 1.9%; placebo: 1.0%). There was no excess in major bleeds with clopidogrel + ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel+ASA vs. 5.3% placebo+ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel+ASA, and 6.3% for placebo+ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel + ASA group (17.4%) vs. the placebo + ASA group (12.9%).The incidence of major bleeding was similar between groups (1.3% versus 1.1% for the clopidogrel + ASA and the placebo + ASA groups, respectively). This was

consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups (0.6% versus 0.5% in the clopidogrel + ASA and the placebo + ASA groups, respectively).

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: 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). Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis

System Organ Class	Common	Uncommon	Rare	Very rare
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

4.9 Overdose

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.
No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC-04.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the

amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

The safety and efficacy of clopidogrel have been evaluated in 4 double-blind studies involving over 80,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75 mg/day or ASA 325 mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p = 0.045), which corresponds, for every 1,000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at p = 0.003) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR = 7.3%; CI: -5.7 to 18.7 [p=0.258]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR = -4.0%; CI: -22.5 to 11.7 [p=0.639]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤75 years.

Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

Acute coronary syndrome

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, N=6,259) or placebo (N=6,303), both given in combination with ASA (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel and placebo was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

The use of clopidogrel in CURE was associated with a decrease in the need of thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel-treated group and 1,187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the clopidogrel-treated group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel treated group and 363 (5.8%) in the placebo treated group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis**.** In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering medicinal products, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily).

In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1,752) or placebo (n=1,739), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients ≥ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint, representing an absolute reduction of 6.7% and a 36 % odds reduction in favor of clopidogrel (95% CI: 24, 47%; p < 0.001), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day, n=22,961) or placebo (n=22,891), in combination with ASA (162 mg/day), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients ≥ 60 years (26% ≥ 70 years) and 54.5% patients who received fibrinolytics.

Clopidogrel significantly reduced the relative risk of death from any cause by 7% (p = 0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

5.2 Pharmacokinetic properties

After repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/l) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative, which represents about 85% of the circulating compound in plasma. Peak plasma levels of this metabolite (approx. 3mg/l after repeated 75 mg oral doses) occurred approximately 1 hour after dosing.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by Cytochrome P_{450} isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

The kinetics of the main circulating metabolite were linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94% respectively). The binding is non-saturable *in vitro* over a wide concentration range.

Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 ml/min) and to levels observed in other studies with healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

The pharmacokinetics and pharmacodynamics of clopidogrel were assessed in a single and multiple dose study in both healthy subjects and those with cirrhosis (Child-Pugh class A or B). Daily dosing for 10 days with clopidogrel 75 mg/day was safe and well tolerated. Clopidogrel C_{max} for both single dose and steady state for cirrhotics was many fold higher than in normal subjects. However, plasma levels of the main circulating metabolite together with the effect of clopidogrel on ADP-induced platelet aggregation and bleeding time were comparable between these groups.

5.3 Preclinical safety data

During non clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.
At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Mannitol (E421)
Macrogol 6000
Microcrystalline cellulose
Hydrogenated castor oil
Low substituted hydroxypropylcellulose

Coating:
Hypromellose (E464)
Lactose
Triacetin (E1518)
Titanium dioxide (E171)
Red iron oxide (E172)
Carnauba wax

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and content of container

Aluminium perforated unit-dose blisters in cardboard cartons containing 4x1, 30x1 and 100x1 film-coated tablets.

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 AUTHORISATION HOLDER

Sanofi Pharma Bristol-Myers Squibb SNC
174 Avenue de France
F-75013 Paris – France

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/069/008 - Cartons of 4x1 film-coated tablets in all aluminium perforated unit-dose blisters
EU/1/98/069/009 - Cartons of 30x1 film-coated tablets in all aluminium perforated unit-dose blisters
EU/1/98/069/010 - Cartons of 100x1 film-coated tablets in all aluminium perforated unit-dose blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 July 1998
Date of latest renewal: 15 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA): http://www.emea.europa.eu/