

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel HCS 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrochloride).

Excipients with known effect:

Each film-coated tablet contains 13 mg of hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, round and slightly convex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary prevention of atherothrombotic events

Clopidogrel is indicated in:

- Adult 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.
- Adult 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.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

For further information please refer to section 5.1.

4.2 Posology and method of administration

Posology

- Adults and elderly (over 65 years)

Clopidogrel should be given as a single daily dose of 75 mg.

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).

In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel (see section 5.1).

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
 - For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.
- Paediatric population
Clopidogrel should not be used in children because of efficacy concerns (see section 5.1).
 - 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).

Method of administration

For oral use.

It may be given with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 2 or section 6.1.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 Special warnings and precautions for use

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, 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 (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or other medicinal products associated with bleeding risk such as pentoxifylline (see section 4.5). 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)

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.

Acquired haemophilia

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Recent ischaemic stroke

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

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2).

CYP2C8 substrates

Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5).

Cross-reactions among thienopyridines

Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section 4.8). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopenia and neutropenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Renal impairment

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).

Hepatic impairment

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).

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk:

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution (see section 4.4).

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). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

Glycoprotein IIb/IIIa inhibitors

Clopidogrel should be used with caution in patients who 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).

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).

SSRIs

Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Other concomitant therapy

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see sections 4.4 and 5.2).

Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton Pump Inhibitors (PPI):

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged (see section 4.4).

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.

The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H₂ blockers or antacids interfere with antiplatelet activity of clopidogrel.

Other medicinal products: 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 coadministration of phenobarbital 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 the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

CYP2C8 substrate medicinal products: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution (see section 4.4).

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 Fertility, pregnancy and lactation

Pregnancy

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).

Breast-feeding

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 Clopidogrel HCS.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

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

Summary of the safety profile

Clopidogrel has been evaluated for safety in more than 44,000 patients who have participated in clinical studies, including over 12,000 patients treated for 1 year or more. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY, COMMIT and ACTIVE-A studies are discussed below. 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 similar for clopidogrel and ASA.

In CURE, there was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the placebo plus ASA group. The incidence of major bleeding was similar between groups. 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.

In ACTIVE-A, the rate of major bleeding was greater in the clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extracranial origin in both groups (5.3% in the clopidogrel + ASA group; 3.5% in the placebo +ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the clopidogrel + ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the clopidogrel + ASA group and 0.7% in the placebo +ASA group) and haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

Tabulated list of adverse reactions

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 ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
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, acquired haemophilia A, granulocytopenia, anaemia
Cardiac disorders				Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*
Immune system disorders				Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)*
Psychiatric disorders				Hallucinations, confusion
Nervous system		Intracranial		Taste disturbances,

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
disorders		bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		ageusia
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, eosinophilic pneumonia
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, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
				eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Reproductive systems and breast disorders			Gynaecomastia	
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		

* Information related to clopidogrel with frequency “not known”.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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: B01AC04.

Mechanism of action

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet

aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y₁₂ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

Pharmacodynamic effects

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.

Clinical efficacy and safety

The safety and efficacy of clopidogrel have been evaluated in 5 double-blind studies involving over 88,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, COMMIT and ACTIVE-A 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 randomized 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.

Atrial fibrillation

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

The ACTIVE-W study demonstrated that anticoagulant treatment with vitamin K antagonists was more effective than with clopidogrel and ASA.

The ACTIVE-A study ($N=7,554$) was a multicenter, randomized, double-blind, placebo-controlled study which compared clopidogrel 75 mg/day + ASA ($N=3,772$) to placebo + ASA ($N=3,782$). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and had at least one of the following risk factors: age ≥ 75 years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction $< 45\%$; or documented peripheral vascular disease. The mean CHADS₂ score was 2.0 (range 0-6).

The major exclusion criteria for patients were documented peptic ulcer disease within the previous 6 months; prior intracerebral hemorrhage; significant thrombocytopenia (platelet count $< 50 \times 10^9/l$); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance to any of the two compounds.

Seventy-three percent (73%) of patients enrolled into the ACTIVE-A study were unable to take VKA due to physician assessment, inability to comply with INR (international normalised ratio) monitoring, predisposition to falling or head trauma, or specific risk of bleeding; for 26% of the patients, the physician's decision was based on the patient's unwillingness to take VKA.

The patient population included 41.8 % women. The mean age was 71 years, 41.6% of patients were ≥ 75 years. A total of 23.0% of patients received anti-arrhythmics, 52.1% beta-blockers, 54.6% ACE inhibitors, and 25.4% statins.

The number of patients who reached the primary endpoint (time to first occurrence of stroke, MI, non-CNS systemic embolism or vascular death) was 832 (22.1%) in the group treated with clopidogrel + ASA and 924 (24.4%) in the placebo + ASA group (relative risk reduction of 11.1%; 95% CI of 2.4% to 19.1%; $p=0.013$), primarily due to a large reduction in the incidence of strokes. Strokes occurred in 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receiving placebo + ASA (relative risk reduction, 28.4%; 95% CI, 16.8% to 38.3%; $p=0.00001$).

Paediatric population

In a dose escalation study of 86 neonates or infants up to 24 months of age at risk for thrombosis (PICOLO), clopidogrel was evaluated at consecutive doses of 0.01, 0.1 and 0.2 mg/kg in neonates and infants and 0.15 mg/kg only in neonates. The dose of 0.2 mg/kg achieved the mean percent inhibition of 49.3% (5 μ M ADP-induced platelet aggregation) which was comparable to that of adults taking Clopidogrel 75 mg/day.

In a randomised, double-blind, parallel-group study (CLARINET), 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomised to receive clopidogrel 0.2 mg/kg ($n=467$) or placebo ($n=439$) along with concomitant background therapy up to the time of second stage surgery. The mean time between shunt palliation and first administration of study medicinal product was 20 days. Approximately 88% of patients received concomitant ASA (range of 1 to 23 mg/kg/day). There was no significant difference between groups in the primary composite endpoint of death, shunt thrombosis or cardiac-related intervention prior to 120 days of age following an event considered of thrombotic nature (89 [19.1%] for the clopidogrel group and 90 [20.5%] for the placebo group) (see section 4.2). Bleeding was the most frequently reported adverse reaction in both clopidogrel and placebo groups; however, there was no significant difference in the bleeding rate between groups. In the long-term safety follow-up of this study, 26 patients with the shunt still in place at one year of age received clopidogrel up to 18 months of age. No new safety concerns were noted during this long-term follow-up.

The CLARINET and the PICOLO trials were conducted using a constituted solution of clopidogrel. In a relative bioavailability study in adults, the constituted solution of clopidogrel showed a similar extent and slightly higher rate of absorption of the main circulating (inactive) metabolite compared to the authorised tablet.

5.2 Pharmacokinetic properties

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Distribution

Clopidogrel and the main circulating (inactive) 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.

Biotransformation

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by

CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The C_{max} of the active metabolite is twice as high following a single 300-mg clopidogrel loading dose as it is after four days of 75-mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing.

Elimination

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. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Pharmacogenetics

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μ M ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 μ M ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1477), and ACTIVE-A (n=601), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Renal impairment

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

Race

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

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

Tablet core:

Cellulose, microcrystalline
Colloidal anhydrous silica
Crospovidone (type A)
Macrogol 6000
Hydrogenated castor oil

Film coating:

Polyvinyl alcohol Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)
Talc
Macrogol 3000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

OPA/Al/PVC-Al blisters containing 28, 30, 50, 56, 84, 90 and 100 film-coated tablets or perforated unit dose blister (OPA/Al/PVC-Al) containing 28x1, 28x1 (calendar pack), 30x1, 50x1, 56x1, 84x1, 90x1 and 100x1 film-coated tablets in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

HCS bvba
H. Kennisstraat 53
B-2650 Edegem
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/651/001	Cartons of 28 film-coated tablets in OPA/Al/PVC - Al blisters
EU/1/10/651/002	Cartons of 30 film-coated tablets in OPA/Al/PVC - Al blisters
EU/1/10/651/003	Cartons of 50 film-coated tablets in OPA/Al/PVC - Al blisters
EU/1/10/651/004	Cartons of 56 film-coated tablets in OPA/Al/PVC - Al blisters
EU/1/10/651/005	Cartons of 84 film-coated tablets in OPA/Al/PVC - Al blisters
EU/1/10/651/006	Cartons of 90 film-coated tablets in OPA/Al/PVC - Al blisters
EU/1/10/651/007	Cartons of 100 film-coated tablets in OPA/Al/PVC - Al blisters
EU/1/10/651/008	Cartons of 28x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters
EU/1/10/651/009	Cartons of 28x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters (calendar pack)
EU/1/10/651/010	Cartons of 30x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters
EU/1/10/651/011	Cartons of 50x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters
EU/1/10/651/012	Cartons of 56x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters
EU/1/10/651/013	Cartons of 84x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters
EU/1/10/651/014	Cartons of 90x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters
EU/1/10/651/015	Cartons of 100x1 film-coated tablets in OPA/Al/PVC - Al perforated unit-dose blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 October 2010

Date of latest renewal: 16 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Krka, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

• **Pharmacovigilance system**

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel HCS 75 mg film-coated tablets
clopidogrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 75 mg of clopidogrel (as hydrochloride).

3. LIST OF EXCIPIENTS

It also contains hydrogenated castor oil.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
28x1 film-coated tablets
30 film-coated tablets
30x1 film-coated tablets
50 film-coated tablets
50x1 film-coated tablets
56 film-coated tablets
56x1 film-coated tablets
84 film-coated tablets
84x1 film-coated tablets
90 film-coated tablets
90x1 film-coated tablets
100 film-coated tablets
100x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

HCS bvba
H. Kennisstraat 53
B-2650 Edegem
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/651/001	28 film-coated tablets
EU/1/10/651/002	30 film-coated tablets
EU/1/10/651/003	50 film-coated tablets
EU/1/10/651/004	56 film-coated tablets
EU/1/10/651/005	84 film-coated tablets
EU/1/10/651/006	90 film-coated tablets
EU/1/10/651/007	100 film-coated tablets
EU/1/10/651/008	28x1 film-coated tablets
EU/1/10/651/009	28x1 film-coated tablets (calendar pack)
EU/1/10/651/010	30x1 film-coated tablets
EU/1/10/651/011	50x1 film-coated tablets
EU/1/10/651/012	56x1 film-coated tablets
EU/1/10/651/013	84x1 film-coated tablets
EU/1/10/651/014	90x1 film-coated tablets
EU/1/10/651/015	100x1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Clopidogrel HCS 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (28, 28x1, 30, 30x1, 50, 50x1, 56, 56x1, 84, 84x1, 90, 90x1, 100, 100x1 film-coated tablets)

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel HCS 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

HCS bvba

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (28x1 film-coated tablets-calendar pack)

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel HCS 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

HCS bvba

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon
Tue
Wed
Thu
Fri
Sat
Sun

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Clopidogrel HCS 75 mg film-coated tablets

Clopidogrel

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you have any side effects, including any side effects not listed in this leaflet, talk to your doctor or pharmacist. See section 4.

What is in this leaflet:

1. What Clopidogrel HCS is and what it is used for
2. What you need to know before you take Clopidogrel HCS
3. How to take Clopidogrel HCS
4. Possible side effects
5. How to store Clopidogrel HCS
6. Contents of the pack and other information

1. What Clopidogrel HCS is and what it is used for

Clopidogrel HCS contains clopidogrel and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood, which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

Clopidogrel HCS is taken by adults to prevent blood clots (thrombi) forming in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Clopidogrel HCS to help prevent blood clots and reduce the risk of these severe events because:

- You have a condition of hardening of arteries (also known as atherosclerosis), and
- You have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease, or
- You have experienced a severe type of chest pain known as 'unstable angina' or 'myocardial infarction' (heart attack). For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. You should also be given acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever as well as to prevent blood clotting) by your doctor.
- You have an irregular heartbeat, a condition called 'atrial fibrillation', and you cannot take medicines known as 'oral anticoagulants' (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. You should have been told that 'oral anticoagulants' are more effective than acetylsalicylic acid or the combined use of Clopidogrel HCS and acetylsalicylic acid for this condition. Your doctor should have prescribed Clopidogrel HCS plus acetylsalicylic acid if you cannot take 'oral anticoagulants' and you do not have a risk of major bleeding.

2. What you need to know before you take Clopidogrel HCS

Do not take Clopidogrel HCS

- If you are allergic to clopidogrel or any of the other ingredients of this medicine (listed in section 6).
- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain,
- If you suffer from severe liver disease.

If you think any of these apply to you, or if you are in any doubt at all, consult your doctor before taking Clopidogrel HCS.

Warnings and precautions

If any of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel HCS:

- if you have a risk of bleeding such as
 - a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer).
 - a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body).
 - a recent serious injury.
 - a recent surgery (including dental).
 - a planned surgery (including dental) in the next seven days.
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred within the last seven days.
- if you have kidney or liver disease.
- if you have had an allergy or reaction to any medicine used to treat your disease.

While you are taking Clopidogrel HCS:

- You should tell your doctor if a surgery (including dental) is planned.
- You should also tell your doctor immediately if you develop a medical condition (also known as Thrombotic Thrombocytopenic Purpura or TTP) that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see section 4 'Possible side effects').
- If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 4 'Possible side effects').
- Your doctor may order blood tests.

Children and adolescents

Do not give this medicine to children (under 12 years of age) because it does not work.

Other medicines and Clopidogrel HCS

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some other medicines may influence the use of Clopidogrel HCS or vice versa.

You should specifically tell your doctor if you take

- medicines that may increase your risk of bleeding such as:
 - o oral anticoagulants, medicines used to reduce blood clotting,
 - o a non-steroidal anti-inflammatory medicine, usually used to treat painful and/or inflammatory conditions of muscle or joints,
 - o heparin, or any other injectable medicine used to reduce blood clotting,
 - o ticlopidine, other antiplatelet agent,
 - o a selective serotonin reuptake inhibitor (including but not restricted to fluoxetine or fluvoxamine), medicines usually used to treat depression,
- omeprazole or esomeprazole, medicines to treat upset stomach,

- fluconazole or voriconazole medicines to treat fungal infections,
- efavirenz, a medicine to treat HIV (human immunodeficiency virus) infections,
- carbamazepine, a medicine to treat some forms of epilepsy,
- moclobemide, medicine to treat depression,
- repaglinide, medicine to treat diabetes,
- paclitaxel, medicine to treat cancer.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed clopidogrel in combination with acetylsalicylic acid, a substance present in many medicines used to relieve pain and lower fever. An occasional use of acetylsalicylic acid (no more than 1,000 mg in any 24 hour period) should generally not cause a problem, but prolonged use in other circumstances should be discussed with your doctor.

Pregnancy and breast-feeding

It is preferable not to take this product during pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Clopidogrel HCS. If you become pregnant while taking Clopidogrel HCS, consult your doctor immediately as it is recommended not to take clopidogrel while you are pregnant.

You should not breast-feed while taking this medicine.

If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Clopidogrel HCS is unlikely to affect your ability to drive or to use machines.

Clopidogrel HCS contains hydrogenated castor oil

This may cause stomach upset or diarrhoea.

3. How to take Clopidogrel HCS

Always take this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

The recommended dose, including for patients with a condition called ‘atrial fibrillation’ (an irregular heartbeat), is one 75 mg tablet of Clopidogrel HCS per day to be taken orally with or without food, and at the same time each day.

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg of Clopidogrel HCS (4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of Clopidogrel HCS per day as described above.

You should take Clopidogrel HCS for as long as your doctor continues to prescribe it.

If you take more Clopidogrel HCS than you should

Contact your doctor or the nearest hospital emergency department because of the increased risk of bleeding.

If you forget to take Clopidogrel HCS

If you forget to take a dose of Clopidogrel HCS, but remember within 12 hours of your usual time, take your tablet straightaway and then take your next tablet at the usual time.

If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

For the 28x1 tablets pack size, you can check the day on which you last took a tablet of Clopidogrel HCS by referring to the calendar printed on the blister.

If you stop taking Clopidogrel HCS

Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:

- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells.
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots and/or confusion (see section 2 'Warnings and precautions').
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

The most common side effect reported with Clopidogrel HCS is bleeding.

Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported.

If you experience prolonged bleeding when taking Clopidogrel HCS

If you cut or injure yourself, it may take slightly longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 2 'Warnings and precautions').

Other side effects include:

Common side effects (may affect up to 1 in 10 people):

Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (may affect up to 1 in 100 people):

Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

Rare side effect (may affect up to 1 in 1000 people):

Vertigo, enlarged breasts in males.

Very rare side effects (may affect up to 1 in 10,000 people):

Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort until fainting); swelling in the mouth; blisters of the skin; skin allergy; sore mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in taste or loss of taste of food.

Side effects with frequency not known (frequency cannot be estimated from the available data):
Hypersensitivity reactions with chest or abdominal pain.

In addition, your doctor may identify changes in your blood or urine test results.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Clopidogrel HCS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister, after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture and light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Clopidogrel HCS contains

The active substance is clopidogrel. Each film-coated tablet contains 75 mg of clopidogrel (as hydrochloride).

The other ingredients are (see section 2 ‘Clopidogrel HCS contains hydrogenated castor oil’):

- Tablet core: microcrystalline cellulose, colloidal anhydrous silica, crospovidone (type A), macrogol 6000 and hydrogenated castor oil.
- Tablet coating: Polyvinyl alcohol, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), talc and macrogol 3000.

What Clopidogrel HCS looks like and contents of the pack

The film-coated tablets are pink, round and slightly convex.

Boxes of 28, 30, 50, 56, 84, 90 or 100 film-coated tablets in blisters or boxes of 28x1, 28x1 (calendar pack), 30x1, 50x1, 56x1, 84x1, 90x1 and 100x1 film-coated tablets in perforated unit dose blisters are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

HCS bvba, H. Kennisstraat 53, B 2650 Edegem, Belgium

Manufacturer

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder

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This leaflet was last revised in <Month YYYY>.

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Plavix 75 mg film-coated tablets
Plavix 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Plavix 75 mg film-coated tablets

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate).

Excipients with known effect:

Each film-coated tablet contains 3 mg of lactose and 3.3 mg of hydrogenated castor oil.

Plavix 300 mg film-coated tablets

Each film-coated tablet contains 300 mg of clopidogrel (as hydrogen sulphate).

Excipients with known effect:

Each film-coated tablet contains 12 mg of lactose and 13.2 mg of hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Plavix 75 mg film-coated tablets

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

Plavix 300 mg film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary prevention of atherothrombotic events

Clopidogrel is indicated in:

- Adult 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.
- Adult 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.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

For further information please refer to section 5.1.

4.2 Posology and method of administration

Posology

- Adults and elderly

Plavix 75 mg film-coated tablets

Clopidogrel should be given as a single daily dose of 75 mg.

Plavix 300 mg film-coated tablets

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).

In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel (see section 5.1).

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
 - For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.
- Paediatric population
Clopidogrel should not be used in children because of efficacy concerns (see section 5.1).
 - 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).

Method of administration

For oral use

It may be given with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 2 or section 6.1.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 Special warnings and precautions for use

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, 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 (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or other medicinal products associated with bleeding risk such as pentoxifylline (see section 4.5). 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)

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.

Acquired haemophilia

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Recent ischaemic stroke

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

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2).

CYP2C8 substrates

Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5).

Cross-reactions among thienopyridines

Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section 4.8). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopenia and neutropenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Renal impairment

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).

Hepatic impairment

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).

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution (see section 4.4).

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). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who 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)

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).

SSRIs: since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Other concomitant therapy: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see sections 4.4 and 5.2).

Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton Pump Inhibitors (PPI):

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged (see section 4.4).

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.

The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

Other medicinal products: 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 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 the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

CYP2C8 substrate medicinal products: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution (see section 4.4).

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 Fertility, pregnancy and lactation

Pregnancy

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).

Breast-feeding

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.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

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

Summary of the safety profile

Clopidogrel has been evaluated for safety in more than 44,000 patients who have participated in clinical studies, including over 12,000 patients treated for 1 year or more. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY, COMMIT and ACTIVE-A studies are discussed below. 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 similar for clopidogrel and ASA.

In CURE, there was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the placebo plus ASA group. The incidence of major bleeding was similar between groups. 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.

In ACTIVE-A, the rate of major bleeding was greater in the clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extracranial origin in both groups (5.3% in the clopidogrel + ASA group; 3.5% in the placebo +ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the clopidogrel + ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the clopidogrel + ASA group and 0.7% in the placebo +ASA group) and haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

Tabulated list of adverse reactions

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 ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
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, acquired haemophilia A, granulocytopenia, anaemia
Cardiac disorders				Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Immune system disorders				Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)*
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances, ageusia
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, eosinophilic pneumonia
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

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Reproductive systems and breast disorders			Gynaecomastia	
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		

* Information related to clopidogrel with frequency “not known”.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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.

Mechanism of action

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y₁₂ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

Pharmacodynamic effects

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.

Clinical efficacy and safety

The safety and efficacy of clopidogrel have been evaluated in 5 double-blind studies involving over 88,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, COMMIT and ACTIVE-A 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 \geq 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 \geq 60 years (26% \geq 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.

Atrial fibrillation

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

The ACTIVE-W study demonstrated that anticoagulant treatment with vitamin K antagonists was more effective than with clopidogrel and ASA.

The ACTIVE-A study (N=7,554) was a multicenter, randomized, double-blind, placebo-controlled study which compared clopidogrel 75 mg/day + ASA (N=3,772) to placebo + ASA (N=3,782). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and had at least one of the following risk factors: age \geq 75 years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction $<$ 45%; or documented peripheral vascular disease. The mean CHADS₂ score was 2.0 (range 0-6).

The major exclusion criteria for patients were documented peptic ulcer disease within the previous 6 months; prior intracerebral hemorrhage; significant thrombocytopenia (platelet count $< 50 \times 10^9/l$); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance to any of the two compounds.

Seventy-three percent (73%) of patients enrolled into the ACTIVE-A study were unable to take VKA due to physician assessment, inability to comply with INR (international normalised ratio) monitoring, predisposition to falling or head trauma, or specific risk of bleeding; for 26% of the patients, the physician's decision was based on the patient's unwillingness to take VKA.

The patient population included 41.8 % women. The mean age was 71 years, 41.6% of patients were ≥ 75 years. A total of 23.0% of patients received anti-arrhythmics, 52.1% beta-blockers, 54.6% ACE inhibitors, and 25.4% statins.

The number of patients who reached the primary endpoint (time to first occurrence of stroke, MI, non-CNS systemic embolism or vascular death) was 832 (22.1%) in the group treated with clopidogrel + ASA and 924 (24.4%) in the placebo + ASA group (relative risk reduction of 11.1%; 95% CI of 2.4% to 19.1%; $p=0.013$), primarily due to a large reduction in the incidence of strokes. Strokes occurred in 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receiving placebo + ASA (relative risk reduction, 28.4%; 95% CI, 16.8% to 38.3%; $p=0.00001$).

Paediatric population

In a dose escalation study of 86 neonates or infants up to 24 months of age at risk for thrombosis (PICOLO), clopidogrel was evaluated at consecutive doses of 0.01, 0.1 and 0.2 mg/kg in neonates and infants and 0.15 mg/kg only in neonates. The dose of 0.2 mg/kg achieved the mean percent inhibition of 49.3% (5 μ M ADP-induced platelet aggregation) which was comparable to that of adults taking Plavix 75 mg/day.

In a randomised, double-blind, parallel-group study (CLARINET), 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomised to receive clopidogrel 0.2 mg/kg ($n=467$) or placebo ($n=439$) along with concomitant background therapy up to the time of second stage surgery. The mean time between shunt palliation and first administration of study medicinal product was 20 days. Approximately 88% of patients received concomitant ASA (range of 1 to 23 mg/kg/day). There was no significant difference between groups in the primary composite endpoint of death, shunt thrombosis or cardiac-related intervention prior to 120 days of age following an event considered of thrombotic nature (89 [19.1%] for the clopidogrel group and 90 [20.5%] for the placebo group) (see section 4.2). Bleeding was the most frequently reported adverse reaction in both clopidogrel and placebo groups; however, there was no significant difference in the bleeding rate between groups. In the long-term safety follow-up of this study, 26 patients with the shunt still in place at one year of age received clopidogrel up to 18 months of age. No new safety concerns were noted during this long-term follow-up.

The CLARINET and the PICOLO trials were conducted using a constituted solution of clopidogrel. In a relative bioavailability study in adults, the constituted solution of clopidogrel showed a similar extent and slightly higher rate of absorption of the main circulating (inactive) metabolite compared to the authorised tablet.

5.2 Pharmacokinetic properties

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Distribution

Clopidogrel and the main circulating (inactive) 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.

Biotransformation

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The C_{max} of the active metabolite is twice as high following a single 300-mg clopidogrel loading dose as it is after four days of 75-mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing.

Elimination

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. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Pharmacogenetics

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μ M ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 µM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1477), and ACTIVE-A (n=601), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Renal impairment

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

Race

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

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 monohydrate
Triacetin (E1518)
Titanium dioxide (E171)
Red iron oxide (E172)

Polishing agent:

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

Plavix 75 mg film-coated tablets

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.

Plavix 300 mg film-coated tablets

Aluminium perforated unit-dose blisters in cardboard cartons containing 4x1, 10x1, 30x1 and 100x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Sanofi Clir SNC
54, rue La Boétie
F-75008 Paris
France

8. MARKETING AUTHORISATION NUMBERS

Plavix 75 mg film-coated tablets

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

Plavix 300 mg film-coated tablets

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
EU/1/98/069/012 - Cartons of 10x1 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

<DD month YYYY>

Detailed information on this medicinal product is available on the website of the European Medicines Agency: <http://www.ema.europa.eu/>

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

- Plavix 75 mg film-coated tablets

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc cedex
France

Delpharm Dijon
6, Boulevard de l'Europe
F-21800 Quétigny
France

Sanofi Synthelabo Limited
Edgefield Avenue
Fawdon
Newcastle upon Tyne NE3 3TT – UK
United Kingdom

Sanofi S.p.A.
Strada Statale 17, Km 22
67019 Scoppito (AQ) – Italy

- Plavix 300 mg film-coated tablets

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambarès & Lagrave
F-33565 Carbon Blanc cedex
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Plavix 75 mg film-coated tablets
clopidogrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 75 mg of clopidogrel (as hydrogen sulphate).

3. LIST OF EXCIPIENTS

It also contains: hydrogenated castor oil and lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
30 film-coated tablets
50x1 film-coated tablets
84 film-coated tablets
90 film-coated tablets
100 film-coated tablets
14 film-coated tablets
7 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30°C (for PVC/PVDC/aluminium blisters)
Or No special storage conditions (for all aluminium blisters)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sanofi Clir SNC
54, rue La Boétie – F-75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/069/001a 28 tablets
EU/1/98/069/001b 28 tablets
EU/1/98/069/002a 50x1 tablets
EU/1/98/069/002b 50x1 tablets
EU/1/98/069/003a 84 tablets
EU/1/98/069/003b 84 tablets
EU/1/98/069/004a 100 tablets
EU/1/98/069/004b 100 tablets
EU/1/98/069/005a 30 tablets
EU/1/98/069/005b 30 tablets
EU/1/98/069/006a 90 tablets
EU/1/98/069/006b 90 tablets
EU/1/98/069/007a 14 tablets
EU/1/98/069/007b 14 tablets
EU/1/98/069/011a 7 tablets
EU/1/98/069/011b 7 tablets

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Plavix 75 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON BLISTERS
(BLISTER / 7, 14, 28 or 84 tablets)

1. NAME OF THE MEDICINAL PRODUCT

Plavix 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Clir SNC

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch:

5. OTHER

Calendar days

Mon

Tue

Wed

Thu

Fri

Sat

Sun

Week 1

Week 2 (for boxes of 14, 28 and 84 tablets)

Week 3 (for boxes of 28 and 84 tablets)

Week 4 (for boxes of 28 and 84 tablets)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER / 30, 50x1, 90 or 100 tablets

1. NAME OF THE MEDICINAL PRODUCT

Plavix 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Clir SNC

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Plavix 300 mg film-coated tablets
clopidogrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg of clopidogrel (as hydrogen sulphate).

3. LIST OF EXCIPIENTS

It also contains: hydrogenated castor oil and lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4x1 film-coated tablets
30x1 film-coated tablets
100x1 film-coated tablets
10x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi Clir SNC
54, rue La Boétie
F-75008 Paris - France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/069/008 4x1 film-coated tablets
EU/1/98/069/009 30x1 film-coated tablets
EU/1/98/069/010 100x1 film-coated tablets
EU/1/98/069/012 10x1 film-coated tablets

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Plavix 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 4x1, 10x1, 30x1 or 100x1 tablets

1. NAME OF THE MEDICINAL PRODUCT

Plavix 300 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi Clir SNC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch:

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Plavix 75 mg film-coated tablets clopidogrel

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you have any side effects, including any side effects not listed in this leaflet, talk to your doctor or pharmacist. See section 4.

What is in this leaflet

1. What Plavix is and what it is used for
2. What you need to know before you take Plavix
3. How to take Plavix
4. Possible side effects
5. How to store Plavix
6. Contents of the pack and other information

1. What Plavix is and what it is used for

Plavix contains clopidogrel and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

Plavix is taken by adults to prevent blood clots (thrombi) forming in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Plavix to help prevent blood clots and reduce the risk of these severe events because:

- You have a condition of hardening of arteries (also known as atherosclerosis), and
- You have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease, or
- You have experienced a severe type of chest pain known as ‘unstable angina’ or ‘myocardial infarction’ (heart attack). For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. You should also be given acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever as well as to prevent blood clotting) by your doctor.
- You have an irregular heartbeat, a condition called ‘atrial fibrillation’, and you cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. You should have been told that ‘oral anticoagulants’ are more effective than acetylsalicylic acid or the combined use of Plavix and acetylsalicylic acid for this condition. Your doctor should have prescribed Plavix plus acetylsalicylic acid if you cannot take ‘oral anticoagulants’ and you do not have a risk of major bleeding.

2. What you need to know before you take Plavix

Do not take Plavix

- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of this medicine (listed in section 6).
- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain.
- If you suffer from severe liver disease.

If you think any of these apply to you, or if you are in any doubt at all, consult your doctor before taking Plavix.

Warnings and precautions

If any of the situations mentioned below apply to you, you should tell your doctor before taking Plavix:

- if you have a risk of bleeding such as
 - a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer).
 - a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body).
 - a recent serious injury.
 - a recent surgery (including dental).
 - a planned surgery (including dental) in the next seven days.
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred within the last seven days.
- if you have kidney or liver disease.
- if you have had an allergy or reaction to any medicine used to treat your disease.

While you are taking Plavix:

- You should tell your doctor if a surgery (including dental) is planned.
- You should also tell your doctor immediately if you develop a medical condition (also known as Thrombotic Thrombocytopenic Purpura or TTP) that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see section 4 'Possible side effects').
- If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 4 'Possible side effects').
- Your doctor may order blood tests.

Children and adolescents

Do not give this medicine to children because it does not work.

Other medicines and Plavix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some other medicines may influence the use of Plavix or vice versa.

You should specifically tell your doctor if you take

- medicines that may increase your risk of bleeding such as:
 - oral anticoagulants, medicines used to reduce blood clotting,
 - a non-steroidal anti-inflammatory medicine, usually used to treat painful and/or inflammatory conditions of muscle or joints,
 - heparin or any other injectable medicine used to reduce blood clotting,
 - ticlopidine, other antiplatelet agent,
 - a selective serotonin reuptake inhibitor (including but not restricted to fluoxetine or fluvoxamine), medicines usually used to treat depression,
- omeprazole or esomeprazole, medicines to treat upset stomach,
- fluconazole or voriconazole, medicines to treat fungal infections,

- efavirenz, a medicine to treat HIV (human immunodeficiency virus) infections,
- carbamazepine, a medicine to treat some forms of epilepsy,
- moclobemide, medicine to treat depression,
- repaglinide, medicine to treat diabetes,
- paclitaxel, medicine to treat cancer.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed Plavix in combination with acetylsalicylic acid, a substance present in many medicines used to relieve pain and lower fever. An occasional use of acetylsalicylic acid (no more than 1,000 mg in any 24 hour period) should generally not cause a problem, but prolonged use in other circumstances should be discussed with your doctor.

Plavix with food and drink

Plavix may be taken with or without food.

Pregnancy and breast-feeding

It is preferable not to take this product during pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Plavix. If you become pregnant while taking Plavix, consult your doctor immediately as it is recommended not to take clopidogrel while you are pregnant.

You should not breast-feed while taking this medicine.

If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Plavix is unlikely to affect your ability to drive or to use machines.

Plavix contains lactose

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicine.

Plavix contains hydrogenated castor oil

This may cause stomach upset or diarrhoea.

3. How to take Plavix

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose, including for patients with a condition called ‘atrial fibrillation’ (an irregular heartbeat), is one 75 mg tablet of Plavix per day to be taken orally with or without food, and at the same time each day.

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg of Plavix (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75-mg tablet of Plavix per day as described above.

You should take Plavix for as long as your doctor continues to prescribe it.

If you take more Plavix than you should

Contact your doctor or the nearest hospital emergency department because of the increased risk of bleeding.

If you forget to take Plavix

If you forget to take a dose of Plavix, but remember within 12 hours of your usual time, take your tablet straightaway and then take your next tablet at the usual time.

If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

For the 7, 14, 28 and 84 tablets pack sizes, you can check the day on which you last took a tablet of Plavix by referring to the calendar printed on the blister.

If you stop taking Plavix

Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:

- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells.
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots and/or confusion (see section 2 'Warnings and precautions').
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

The most common side effect reported with Plavix is bleeding. Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported.

If you experience prolonged bleeding when taking Plavix

If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 2 'Warnings and precautions').

Other side effects include:

Common side effects (may affect up to 1 in 10 people):

Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (may affect up to 1 in 100 people):

Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

Rare side effect (may affect up to 1 in 1000 people):

Vertigo, enlarged breasts in males.

Very rare side effects (may affect up to 1 in 10,000 people):

Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions (for example, overall sensation of heat with

sudden general discomfort until fainting); swelling in the mouth; blisters of the skin; skin allergy; sore mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in taste or loss of taste of food.

Side effects with frequency not known (frequency cannot be estimated from the available data):
Hypersensitivity reactions with chest or abdominal pain.

In addition, your doctor may identify changes in your blood or urine test results.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Plavix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister, after EXP. The expiry date refers to the last day of that month.

Refer to the storage conditions on the carton.

If Plavix is supplied in PVC/PVDC/aluminium blisters, store below 30°C.

If Plavix is supplied in all aluminium blisters, it does not require any special storage conditions.

Do not use this medicine if you notice any visible sign of deterioration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information

What Plavix contains

The active substance is clopidogrel. Each tablet contains 75 mg of clopidogrel (as hydrogen sulphate).

The other ingredients are (see section 2 'Plavix contains lactose' and 'Plavix contains hydrogenated castor oil'):

- Tablet core: mannitol (E421), hydrogenated castor oil, microcrystalline cellulose, macrogol 6000 and low-substituted hydroxypropylcellulose,
- Tablet coating: lactose monohydrate (milk sugar), hypromellose (E464), triacetin (E1518), red iron oxide (E172) and titanium dioxide (E171),
- Polishing agent: carnauba wax.

What Plavix looks like and contents of the pack

Plavix 75-mg film-coated tablets are round, biconvex, pink, engraved on one side with the number '75' and on the other side with the number '1171'. Plavix is supplied in cardboard cartons containing:

- 7, 14, 28, 30, 84, 90 and 100 tablets in PVC/PVDC/Aluminium blisters or in all aluminium blisters
- 50x1 tablets in PVC/PVDC/Aluminium blisters or in all aluminium perforated unit-dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturers

Marketing Authorisation Holder: Sanofi Clir SNC
54, rue La Boétie - F-75008 Paris - France

Manufacturers:

Sanofi Winthrop Industrie

1, rue de la Vierge, Ambarès & Lagrave, F-33565 Carbon Blanc cedex, France
or

Sanofi-Synthelabo Limited,
Edgefield Avenue, Fawdon

Newcastle Upon Tyne, Tyne & Wear NE3 3TT - UK, United Kingdom
or

Delpharm Dijon

6, boulevard de l'Europe, F-21800 Quétigny, France
or

Sanofi S.p.A.

Strada Statale 17, Km 22

67019 Scoppito (AQ) – Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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United Kingdom

Sanofi
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This leaflet was last revised in <Month YYYY>.

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu/>

Package leaflet: Information for the user

Plavix 300-mg film-coated tablets clopidogrel

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you have any side effects, including any side effects not listed in this leaflet, talk to your doctor or pharmacist. See section 4.

What is in this leaflet

1. What Plavix is and what it is used for
2. What you need to know before you take Plavix
3. How to take Plavix
4. Possible side effects
5. How to store Plavix
6. Contents of the pack and other information

1. What Plavix is and what it is used for

Plavix contains clopidogrel and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

Plavix is taken by adults to prevent blood clots (thrombi) forming in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Plavix to help prevent blood clots and reduce the risk of these severe events because:

- You have a condition of hardening of arteries (also known as atherosclerosis), and
- You have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease, or
- You have experienced a severe type of chest pain known as ‘unstable angina’ or ‘myocardial infarction’ (heart attack). For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. You should also be given acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever as well as to prevent blood clotting) by your doctor.
- You have an irregular heartbeat, a condition called ‘atrial fibrillation’, and you cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. You should have been told that ‘oral anticoagulants’ are more effective than acetylsalicylic acid or the combined use of Plavix and acetylsalicylic acid for this condition. Your doctor should have prescribed Plavix plus acetylsalicylic acid if you cannot take ‘oral anticoagulants’ and you do not have a risk of major bleeding.

2. What you need to know before you take Plavix

Do not take Plavix:

- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of this medicine (listed in section 6).
- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain.
- If you suffer from severe liver disease.

If you think any of these apply to you, or if you are in any doubt at all, consult your doctor before taking Plavix.

Warnings and precautions

If any of the situations mentioned below apply to you, you should tell your doctor before taking Plavix:

- if you have a risk of bleeding such as
 - a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer).
 - a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body).
 - a recent serious injury.
 - a recent surgery (including dental).
 - a planned surgery (including dental) in the next seven days.
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred within the last seven days.
- if you have kidney or liver disease.
- if you have had an allergy or reaction to any medicine used to treat your disease.

While you are taking Plavix:

- You should tell your doctor if a surgery (including dental) is planned.
- You should also tell your doctor immediately if you develop a medical condition (also known as Thrombotic Thrombocytopenic Purpura or TTP) that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see section 4 'Possible side effects').
- If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 4 'Possible side effects').
- Your doctor may order blood tests.

Children and adolescents

Do not give this medicine to children because it does not work.

Other medicines and Plavix

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some other medicines may influence the use of Plavix or vice versa.

You should specifically tell your doctor if you take

- medicines that may increase your risk of bleeding such as:
 - o oral anticoagulants, medicines used to reduce blood clotting,
 - o a non-steroidal anti-inflammatory medicine, usually used to treat painful and/or inflammatory conditions of muscle or joints,
 - o heparin or any other injectable medicine used to reduce blood clotting,
 - o ticlopidine, other antiplatelet agent,
 - o a selective serotonin reuptake inhibitor (including but not restricted to fluoxetine or fluvoxamine), medicines usually used to treat depression,
- omeprazole or esomeprazole, medicines to treat upset stomach,
- fluconazole or voriconazole, medicines to treat fungal infections,
- efavirenz, a medicine to treat HIV (human immunodeficiency virus) infections,

- carbamazepine, a medicine to treat some forms of epilepsy,
- moclobemide, medicine to treat depression,
- repaglinide, medicine to treat diabetes,
- paclitaxel, medicine to treat cancer.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed Plavix in combination with acetylsalicylic acid, a substance present in many medicines used to relieve pain and lower fever. An occasional use of acetylsalicylic acid (no more than 1,000 mg in any 24 hour period) should generally not cause a problem, but prolonged use in other circumstances should be discussed with your doctor.

Plavix with food and drink

Plavix may be taken with or without food.

Pregnancy and breast-feeding

It is preferable not to take this product during pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Plavix. If you become pregnant while taking Plavix, consult your doctor immediately as it is recommended not to take clopidogrel while you are pregnant.

You should not breast-feed while taking this medicine.

If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Plavix is unlikely to affect your ability to drive or to use machines.

Plavix contains lactose

If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicine.

Plavix contains hydrogenated castor oil

This may cause stomach upset or diarrhoea.

3. How to take Plavix

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose, including for patients with a condition called 'atrial fibrillation' (an irregular heartbeat), is one 75 mg tablet of Plavix per day to be taken orally with or without food, and at the same time each day.

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg of Plavix (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of Plavix per day as described above.

You should take Plavix for as long as your doctor continues to prescribe it.

If you take more Plavix than you should

Contact your doctor or the nearest hospital emergency department because of the increased risk of bleeding.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:

- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells.
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots, and/or confusion (see section 2 'Warnings and precautions').
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

The most common side effect reported with Plavix is bleeding. Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported.

If you experience prolonged bleeding when taking Plavix

If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 2 'Warnings and precautions').

Other side effects include:

Common side effects (may affect up to 1 in 10 people):

Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (may affect up to 1 in 100 people):

Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

Rare side effect (may affect up to 1 in 1000 people):

Vertigo, enlarged breasts in males.

Very rare side effects (may affect up to 1 in 10,000 people):

Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort until fainting); swelling in the mouth; blisters of the skin; skin allergy; sore mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in taste or loss of taste of food.

Side effects with frequency not known (frequency cannot be estimated from the available data):

Hypersensitivity reactions with chest or abdominal pain.

In addition, your doctor may identify changes in your blood or urine test results.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Plavix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister, after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not use this medicine if you notice any visible sign of deterioration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information

What Plavix contains

The active substance is clopidogrel. Each tablet contains 300 mg of clopidogrel (as hydrogen sulphate).

The other ingredients are (see section 2 'Plavix contains lactose' and 'Plavix contains hydrogenated castor oil'):

- Tablet core: mannitol (E421), hydrogenated castor oil, microcrystalline cellulose, macrogol 6000 and low-substituted hydroxypropylcellulose
- Tablet coating: lactose monohydrate (milk sugar), hypromellose (E464), triacetin (E1518), red iron oxide (E172) and titanium dioxide (E171),
- Polishing agent: carnauba wax.

What Plavix looks like and contents of the pack

Plavix 300-mg film-coated tablets are oblong, pink, engraved on one side with the number '300' and on the other side with the number '1332'. Plavix is supplied in cardboard cartons containing 4x1, 10x1, 30x1 and 100x1 tablets in all aluminium perforated unit-dose blisters. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer:
Sanofi Winthrop Industrie
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This leaflet was last revised in <Month YYYY>.

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu/>