ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel BMS 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

For further information please refer to section 5.1.

4.2 Posology and method of administration

- Adults and elderly

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

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

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

- Pharmacogenetics
  CYP2C19 poor metaboliser status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolisers has yet to be determined (see section 5.2).

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function (see section 5.2).

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2). Although the evidence of CYP2C19 inhibition varies within the class of Proton Pump Inhibitors, clinical studies suggest an interaction between clopidogrel and possibly all members of this class. Therefore, concomitant use of Proton Pump Inhibitors should be avoided unless absolutely necessary. There is no evidence that other drugs that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

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

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

Clopidogrel BMS 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

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

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

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

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

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

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

Other concomitant therapy:
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 should be discouraged (see sections 4.4 and 5.2).

Drugs that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

Proton Pump Inhibitors:
Although the evidence of CYP2C19 inhibition varies within the class of Proton Pump Inhibitors, clinical studies suggest an interaction between clopidogrel and possibly all members of this class. Therefore, concomitant use of Proton Pump Inhibitors should be avoided unless absolutely necessary. There is no evidence that other drugs that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

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

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

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

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

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

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

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis
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
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Clopidogrel 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 $P2Y_{12}$ 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 drugs, not all patients will have adequate platelet inhibition.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At

steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

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

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

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

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

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

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

Acute coronary syndrome

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

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events

(primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

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

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

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

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

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

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

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

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

or death. The population included 27.8% women, 58.4% patients ≥ 60 years (26% ≥ 70 years) and 54.5% patients who received fibrinolytics.

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

5.2 Pharmacokinetic properties

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.

Metabolism
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. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

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
Several polymorphic CYP450 enzymes activate clopidogrel. 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 correspond to reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for 85% of reduced function alleles in whites and 99% in Asians. Other alleles associated with reduced metabolism include CYP2C19*4, *5, *6, *7, and *8, but these are less frequent in the general population. Published frequencies for the common CYP2C19 phenotypes and genotypes are listed in the table below.

CYP2C19 Phenotype and Genotype Frequency

	Frequency (%)		
	White (n=1356)	**Black (n=966)**	**Chinese (n=573)**
Extensive metabolism: CYP2C19*1/*1	74	66	38
Intermediate metabolism: CYP2C19*1/*2 or *1/*3	26	29	50
Poor metabolism: CYP2C19*2/*2, *2/*3 or *3/*3	2	4	14

To date, the impact of CYP2C19 genotype on the pharmacokinetics of the active metabolite of clopidogrel has been evaluated in 227 subjects from 7 reported studies. Reduced CYP2C19 metabolism in intermediate and poor metabolisers decreased the C_{max} and AUC of the active metabolite by 30-50% following 300- or 600-mg loading doses and 75-mg maintenance doses. Lower active metabolite exposure results in less platelet inhibition or higher residual platelet reactivity. To date, diminished antiplatelet responses to clopidogrel have been described for intermediate and poor metabolisers in 21 reported studies involving 4,520 subjects. The relative difference in antiplatelet response between genotype groups varies across studies depending on the method used to evaluate response, but is typically greater than 30%.

The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post hoc clinical trial analyses (substudies of CLARITY [n=465] and TRITON-TIMI 38 [n=1,477]) and 5 cohort studies (total n=6,489). In CLARITY and one of the cohort studies (n=765; Trenk), cardiovascular event rates did not differ significantly by genotype. In TRITON-TIMI 38 and 3 of the cohort studies (n= 3,516; Collet, Sibbing, Giusti), patients with an impaired metaboliser status (intermediate and poor combined) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers. In the fifth cohort study (n=2,208; Simon), the increased event rate was observed only in poor metabolisers.

Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity.

There may be genetic variants of other CYP450 enzymes with effects on the ability to form the active metabolite of clopidogrel.

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
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

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bristol Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/08/464/001 - Cartons of 14 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/002 - Cartons of 14 film-coated tablets in all aluminium blisters
EU/1/08/464/003 - Cartons of 28 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/004 - Cartons of 28 film-coated tablets in all aluminium blisters
EU/1/08/464/005 - Cartons of 30 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/006 - Cartons of 30 film-coated tablets in all aluminium blisters
EU/1/08/464/007 - Cartons of 50x1 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/008 - Cartons of 50x1 film-coated tablets in all aluminium blisters
EU/1/08/464/009 - Cartons of 84 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/010 - Cartons of 84 film-coated tablets in all aluminium blisters
EU/1/08/464/011 - Cartons of 90 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/012 - Cartons of 90 film-coated tablets in all aluminium blisters
EU/1/08/464/013 - Cartons of 100 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/014 - Cartons of 100 film-coated tablets in all aluminium blisters
EU/1/08/464/018 - Cartons of 7 film-coated tablets in PVC/PVDC/Alu blisters
EU/1/08/464/019 - Cartons of 7 film-coated tablets in all aluminium blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 July 2008

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel BMS 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

For further information please refer to section 5.1.

4.2 Posology and method of administration

- Adults and elderly

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

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

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

- Pharmacogenetics
  CYP2C19 poor metaboliser status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolisers has yet to be determined (see section 5.2).

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

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function (see section 5.2).

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2). Although the evidence of CYP2C19 inhibition varies within the class of Proton Pump Inhibitors, clinical studies suggest an interaction between clopidogrel and possibly all members of this class. Therefore, concomitant use of Proton Pump Inhibitors should be avoided unless absolutely necessary. There is no evidence that other drugs that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

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

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

Clopidogrel BMS 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

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

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

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

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

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

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

Other concomitant therapy:
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 should be discouraged (see sections 4.4 and 5.2).

Drugs that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

Proton Pump Inhibitors:
Although the evidence of CYP2C19 inhibition varies within the class of Proton Pump Inhibitors, clinical studies suggest an interaction between clopidogrel and possibly all members of this class. Therefore, concomitant use of Proton Pump Inhibitors should be avoided unless absolutely necessary. There is no evidence that other drugs that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

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

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

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

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

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

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

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis
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
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Clopidogrel 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 $P2Y_{12}$ 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 drugs, not all patients will have adequate platelet inhibition.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At

steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

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

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

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

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

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

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

Acute coronary syndrome

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

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events

(primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

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

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

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

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

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

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

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

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

or death. The population included 27.8% women, 58.4% patients ≥ 60 years (26% ≥ 70 years) and 54.5% patients who received fibrinolytics.

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

5.2 Pharmacokinetic properties

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.

Metabolism
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. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

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
Several polymorphic CYP450 enzymes activate clopidogrel. 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 correspond to reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for 85% of reduced function alleles in whites and 99% in Asians. Other alleles associated with reduced metabolism include CYP2C19*4, *5, *6, *7, and *8, but these are less frequent in the general population. Published frequencies for the common CYP2C19 phenotypes and genotypes are listed in the table below.

CYP2C19 Phenotype and Genotype Frequency

	Frequency (%)		
	White (n=1356)	**Black (n=966)**	**Chinese (n=573)**
Extensive metabolism: CYP2C19*1/*1	74	66	38
Intermediate metabolism: CYP2C19*1/*2 or *1/*3	26	29	50
Poor metabolism: CYP2C19*2/*2, *2/*3 or *3/*3	2	4	14

To date, the impact of CYP2C19 genotype on the pharmacokinetics of the active metabolite of clopidogrel has been evaluated in 227 subjects from 7 reported studies. Reduced CYP2C19 metabolism in intermediate and poor metabolisers decreased the C_{max} and AUC of the active metabolite by 30-50% following 300- or 600-mg loading doses and 75-mg maintenance doses. Lower active metabolite exposure results in less platelet inhibition or higher residual platelet reactivity. To date, diminished antiplatelet responses to clopidogrel have been described for intermediate and poor metabolisers in 21 reported studies involving 4,520 subjects. The relative difference in antiplatelet response between genotype groups varies across studies depending on the method used to evaluate response, but is typically greater than 30%.

The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post hoc clinical trial analyses (substudies of CLARITY [n=465] and TRITON-TIMI 38 [n=1,477]) and 5 cohort studies (total n=6,489). In CLARITY and one of the cohort studies (n=765; Trenk), cardiovascular event rates did not differ significantly by genotype. In TRITON-TIMI 38 and 3 of the cohort studies (n= 3,516; Collet, Sibbing, Giusti), patients with an impaired metaboliser status (intermediate and poor combined) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers. In the fifth cohort study (n=2,208; Simon), the increased event rate was observed only in poor metabolisers.

Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity.

There may be genetic variants of other CYP450 enzymes with effects on the ability to form the active metabolite of clopidogrel.

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
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

This medicinal product does not require any special storage conditions.

6.5 Nature and content of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bristol Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/08/464/015 - Cartons of 4x1 film-coated tablets in all aluminium perforated unit-dose blisters
EU/1/08/464/016 - Cartons of 30x1 film-coated tablets in all aluminium perforated unit-dose blisters
EU/1/08/464/017 - Cartons of 100x1 film-coated tablets in all aluminium perforated unit-dose blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 July 2008

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

- Clopidogrel BMS 75 mg film-coated tablets

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

Sanofi Winthrop Industrie
6, Boulevard de l'Europe
F-21800 Quétigny
France

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

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.

- Clopidogrel BMS 300 mg film-coated tablets

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 dated 25 September 2007 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel BMS 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

Oral use
Read the package leaflet before use.

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

Keep out of the reach and sight 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

Bristol Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/464/001 14 tablets
EU/1/08/464/002 14 tablets
EU/1/08/464/003 28 tablets
EU/1/08/464/004 28 tablets
EU/1/08/464/005 30 tablets
EU/1/08/464/006 30 tablets
EU/1/08/464/007 50x1 tablets
EU/1/08/464/008 50x1 tablets
EU/1/08/464/009 84 tablets
EU/1/08/464/010 84 tablets
EU/1/08/464/011 90 tablets
EU/1/08/464/012 90 tablets
EU/1/08/464/013 100 tablets
EU/1/08/464/014 100 tablets
EU/1/08/464/018 7 tablets
EU/1/08/464/019 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

Clopidogrel BMS 75 mg

PARTICULARS TO APPEAR ON BLISTERS
(boxes of 7, 14, 28 or 84 tablets)

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel BMS 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol Myers Squibb Pharma EEIG

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/Boxes of 30, 50x1, 90 or 100 tablets

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel BMS 75 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol Myers Squibb Pharma EEIG

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

Clopidogrel BMS 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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

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

Keep out of the reach and sight 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

Bristol Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/464/015 4x1 film-coated tablets
EU/1/08/464/016 30x1 film-coated tablets
EU/1/08/464/017 100x1 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

CLOPIDOGREL BMS 300 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER / Box of 4x1, 30x1 or 100x1 tablets

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel BMS 300 mg film-coated tablets
clopidogrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol Myers Squibb Pharma EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch:

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clopidogrel BMS 75 mg film-coated tablets
clopidogrel

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CLOPIDOGREL BMS IS AND WHAT IT IS USED FOR

Clopidogrel BMS belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood, smaller than red or white blood cells, 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 BMS is taken 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 BMS 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.

2. BEFORE YOU TAKE CLOPIDOGREL BMS

Do not take Clopidogrel BMS:
- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of Clopidogrel BMS;
- 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 BMS.

Take special care with Clopidogrel BMS:
If any of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel BMS:

- 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 are taking another type of medicine (see 'Taking other medicines').
- if you have kidney or liver disease

While you are taking Clopidogrel BMS:

- 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 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.
- You should tell your doctor or pharmacist if you notice any side effect not listed in section 4 'POSSIBLE SIDE EFFECTS' or if you notice that a side effect gets serious.

Clopidogrel BMS is not intended for use in children or adolescents.

Taking other medicines:
Some other medicines may influence the use of Clopidogrel BMS or vice versa.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The use of oral anticoagulants (medicines used to reduce blood clotting) with Clopidogrel BMS is not recommended.

You should specifically tell your doctor if you take a non-steroidal anti-inflammatory drug, usually used to treat painful and/or inflammatory conditions of muscle or joints, or if you take heparin or any other medicine used to reduce blood clotting, or if you take a proton pump inhibitor (e.g, omeprazole) for upset stomach.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed Clopidogrel BMS 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.

Taking Clopidogrel BMS with food and drink
Clopidogrel BMS may be taken with or without food.

Pregnancy and breast-feeding
It is preferable not to use this product during pregnancy and breast-feeding.

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

While taking Clopidogrel BMS, consult your doctor about the breast-feeding of a baby.

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

Driving and using machines:
Clopidogrel BMS is unlikely to affect your ability to drive or to use machines.

Important information about some of the ingredients of Clopidogrel BMS:
Clopidogrel BMS 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.

Clopidogrel BMS also contains hydrogenated castor oil which may cause stomach upset or diarrhoea.

3. HOW TO TAKE CLOPIDOGREL BMS

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

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg of Clopidogrel BMS (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the usual dose is one 75-mg tablet of Clopidogrel BMS per day to be taken orally with or without food, and at the same time each day.

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

If you take more Clopidogrel BMS 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 BMS:
If you forget to take a dose of Clopidogrel BMS, 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 the forgotten individual doses.

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

If you stop taking Clopidogrel BMS:
Do not stop the treatment. Contact your doctor or pharmacist before stopping.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clopidogrel BMS 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 'Take special care with Clopidogrel BMS').
- 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 (affects 1 to 10 patients in 100) **reported with Clopidogrel BMS 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 BMS
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 'Take special care with Clopidogrel BMS').

Other side effects reported with Clopidogrel BMS are:
Common side effects (affects 1 to 10 patients in 100): Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (affects 1 to 10 patients in 1,000): Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

Rare side effect (affects 1 to 10 patients in 10,000): Vertigo.

Very rare side effects (affects less than 1 patient in 10,000): Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions; swelling in the mouth; blisters of the skin; skin allergy; inflammation of the mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in the way things taste.

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CLOPIDOGREL BMS

Keep out of the reach and sight of children.
Do not use Clopidogrel BMS after the expiry date which is stated on the carton and on the blister.

Refer to the storage conditions on the carton.
If Clopidogrel BMS is supplied in PVC/PVDC/aluminium blisters, store below 30°C.
If Clopidogrel BMS is supplied in all aluminium blisters, it does not require any special storage conditions.
Do not use Clopidogrel BMS if you notice any visible sign of deterioration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

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

The other ingredients are mannitol (E421), hydrogenated castor oil, microcrystalline cellulose, macrogol 6000 and low-substituted hydroxypropylcellulose in the tablet core, and lactose (milk sugar), hypromellose (E464), triacetin (E1518), red iron oxide (E172), titanium dioxide (E171), and carnauba wax in the tablet coating.

What Clopidogrel BMS looks like and contents of the pack

Clopidogrel BMS 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'. Clopidogrel BMS 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, or 50x1 tablets in PVC/PVDC/Aluminium blisters or in all aluminium perforated unit-dose blisters. Not all pack sizes may be marketed.

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This leaflet was last approved in MM/YYYY

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clopidogrel BMS 300-mg film-coated tablets
clopidogrel

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CLOPIDOGREL BMS IS AND WHAT IT IS USED FOR

Clopidogrel BMS belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood, smaller than red or white blood cells, 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 BMS is taken 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 BMS 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.

2. BEFORE YOU TAKE CLOPIDOGREL BMS

Do not take Clopidogrel BMS:

- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients of Clopidogrel BMS;
- 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 BMS.

Take special care with Clopidogrel BMS:
If any of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel BMS:

- 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 (ischemic stroke) which occurred within the last seven days
- if you are taking another type of medicine (see 'Taking other medicines').
- if you have kidney or liver disease

While you are taking Clopidogrel BMS:

- 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 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.
- You should tell your doctor or pharmacist if you notice any side effect not listed in section 4 'POSSIBLE SIDE EFFECTS' or if you notice that a side effect gets serious.

Clopidogrel BMS is not intended for use in children or adolescents.

Taking other medicines:
Some other medicines may influence the use of Clopidogrel BMS or vice versa.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The use of oral anticoagulants (medicines used to reduce blood clotting) with Clopidogrel BMS is not recommended.

You should specifically tell your doctor if you take a non-steroidal anti-inflammatory drug, usually used to treat painful and/or inflammatory conditions of muscle or joints, or if you take heparin or any other medicine used to reduce blood clotting, or if you take a proton pump inhibitor (e.g, omeprazole) for upset stomach.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed Clopidogrel BMS 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.

Taking Clopidogrel BMS with food and drink
Clopidogrel BMS may be taken with or without food.

Pregnancy and breast-feeding
It is preferable not to use this product during pregnancy and breast-feeding.

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

While taking Clopidogrel BMS, consult your doctor about the breast-feeding of a baby.

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

Driving and using machines:
Clopidogrel BMS is unlikely to affect your ability to drive or to use machines.

Important information about some of the ingredients of Clopidogrel BMS:
Clopidogrel BMS 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.

Clopidogrel BMS also contains hydrogenated castor oil which may cause stomach upset or diarrhoea.

3. HOW TO TAKE CLOPIDOGREL BMS

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

If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 300 mg of Clopidogrel BMS (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the usual dose is one 75 mg tablet of Clopidogrel BMS per day to be taken orally with or without food, and at the same time each day.

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

If you take more Clopidogrel BMS 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clopidogrel BMS 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 'Take special care with Clopidogrel BMS').
- 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 (affects 1 to 10 patients in 100) **reported with Clopidogrel BMS 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 BMS
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 'Take special care with Clopidogrel BMS').

Other side effects reported with Clopidogrel BMS are:
Common side effects (affects 1 to 10 patients in 100): Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (affects 1 to 10 patients in 1,000): Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness.

Rare side effect (affects 1 to 10 patients in 10,000): Vertigo.

Very rare side effects (affects less than 1 patient in 10,000): Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions; swelling in the mouth; blisters of the skin; skin allergy; inflammation of the mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in the way things taste.

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CLOPIDOGREL BMS

Keep out of the reach and sight of children.
Do not use Clopidogrel BMS after the expiry date which is stated on the carton and on the blister.
This medicinal product does not require any special storage conditions.

Do not use Clopidogrel BMS if you notice any visible sign of deterioration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

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

The other ingredients are mannitol (E421), hydrogenated castor oil, microcrystalline cellulose, macrogol 6000 and low-substituted hydroxypropylcellulose in the tablet core, and lactose (milk sugar), hypromellose (E464), triacetin (E1518), red iron oxide (E172), titanium dioxide (E171), and carnauba wax in the tablet coating.

What Clopidogrel BMS looks like and contents of the pack

Clopidogrel BMS 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'. Clopidogrel BMS is supplied in cardboard cartons containing 4x1, 30x1 and 100x1 tablets in all aluminium perforated unit-dose blisters. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder:
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Uxbridge Business Park
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Manufacturer:
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1, rue de la Vierge, Ambarès & Lagrave, F-33565 Carbon Blanc cedex, France

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

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