Plavix®

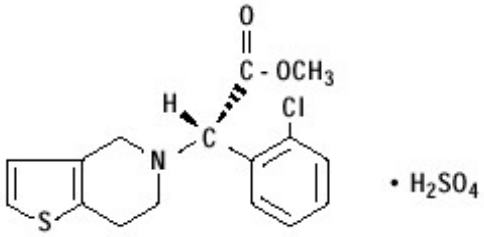
1. NAME OF MEDICINAL PRODUCT

1.1 Product name: Plavix (75 mg) (Clopidogrel hydrogen sulfate)
1.2 Strength: 75 mg
1.3 Pharmaceutical dosage form: film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Clopidogrel hydrogen sulfate is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically it is methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1). The empirical formula of clopidogrel hydrogen sulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9.
The structural formula is as follows:



Clopidogrel hydrogen sulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves slightly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

2.2 Quantitative Declaration

Active ingredient:
Plavix (75 mg): clopidogrel hydrogen sulfate 75 mg
Clopidogrel hydrogen sulfate 97.875 mg (molar equivalent of 75 mg of clopidogrel base)

3. PHARMACEUTICAL FORM

Film-coated tablet.
Plavix 75 mg film-coated tablets are pink, round, biconvex, film-coated, and 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 secondary prevention of atherothrombotic events in:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic 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).
  - ST segment elevation acute myocardial infarction, in combination with ASA in patients undergoing percutaneous coronary intervention (including patients undergoing a stent placement) or medically treated patients eligible for thrombolytic/fibrinolytic therapy.
  - Patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).

- In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)

  Clopidogrel in combination with ASA is indicated in:
  - Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) within 24 hours of either the TIA or IS event.

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

- Atrial fibrillation (AF)
  In patients with atrial fibrillation (AF) at increased risk of vascular events who can take vitamin K antagonist (VKA) therapy, VKA has been shown to be associated with a better clinical benefit than acetylsalicylic acid (ASA) alone or the combination of clopidogrel and ASA for the reduction of stroke.

  In patients with atrial fibrillation who have at least one risk factor for vascular events and who cannot take VKA therapy (e.g., specific risk of bleeding, physician assessment that patient is unable to comply with INR (international normalized ratio) monitoring or that VKA use is inappropriate), clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke. Clopidogrel in combination with ASA has been shown to reduce the rate of the combined endpoint of stroke, myocardial infarction (MI), non-CNS systemic embolism, or vascular death, largely through a reduction in stroke (see *Pharmacological Properties, Pharmacodynamic properties*).

For further information please refer to *Pharmacodynamic properties*.

4.2 Posology and method of administration

Posology:
Adults and elderly
Plavix 75 mg film-coated tablets
Clopidogrel should be given as a single daily dose of 75 mg with or without food.

- 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 or 600 mg loading dose. A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended (see section *Special warnings and special precautions for use*). Clopidogrel treatment should be 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 *Pharmacodynamic properties*).
  ST segment elevation acute myocardial infarction: For medically treated patients eligible for thrombolytic/fibrinolytic therapy, clopidogrel should be given as a single daily dose of 75 mg initiated with or without a loading dose in combination with ASA and with or without thrombolytics (see *Pharmacodynamic properties*). For patients greater than 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 *Pharmacodynamic properties*).
  When percutaneous coronary intervention (PCI) is intended: Clopidogrel should be initiated at a loading dose of 600 mg in patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy. In patients ≥ 75 years old the 600 mg LD should be administered with caution (see *Special warning and special precautions for use*). Clopidogrel 300 mg loading dose should be given in patients undergoing PCI within 24 hours of receiving fibrinolytic therapy.
  Clopidogrel treatment should be continued at 75 mg once a day with ASA 75 mg – 100 mg daily. Combined therapy should be started as early as possible after symptoms start and continued up to 12 months (see *Pharmacodynamic properties*).

Adult patients with moderate to high-risk TIA or minor IS

- Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA (75 mg - 100 mg once daily). Treatment

with clopidogrel and ASA should be started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy.

Atrial Fibrillation

- Clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel (see *Pharmacological Properties, Pharmacodynamic properties*).

Children and adolescents

Safety and effectiveness in pediatric populations have not been established (see *Pharmacodynamic properties*).

Elderly patients

Non-ST segments elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended (see *Special warning and special precautions for use*).

ST segment elevation acute myocardial infarction: For medically treated patients eligible for thrombolytic/fibrinolytic therapy: in patients over 75 years of age clopidogrel should be initiated without a loading dose.

For patients undergoing primary PCI and in patients undergoing PCI more than 24 hours of receiving fibrinolytic therapy: In patients ≥ 75 years old the 600 mg LD should be administered with caution (see *Special warning and special precautions for use*).

For a loading dose in patients ≥75 years of age, see section *Special warnings and special precautions for use.*

Pharmacogenetics

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. A higher dose regimen (600-mg loading dose followed by 150 mg once daily) in poor metabolisers increases antiplatelet response (see *Pharmacokinetics properties, Pharmacogenetics*). Consider the use of higher clopidogrel doses in patients who are poor CYP2C19 metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Renal impairment

Therapeutic experience is limited in patients with renal impairment (see section *Special warnings and special precautions for use*).

Hepatic impairment

Therapeutic experience is limited in patients with severe hepatic disease who may have bleeding diatheses (see *Special warnings and special precautions for use*).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the medicinal product.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
- Breast-feeding (see *Pregnancy and Lactation*).

4.4 Special warnings and special precautions for use

- ***Bleeding and haematological disorders***

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever such suspected clinical symptoms suggestive of bleeding arise during the course of treatment (see *Undesirable effects*).

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, non-steroidal anti-inflammatory drugs (NSAIDs), or selective serotonin reuptake inhibitors (SSRIs)), or CYP2C19 strong inducers. Due to the increased risk of hemorrhage, triple antiplatelet therapy (clopidogrel + aspirin + dipyridamole) for stroke secondary prevention is not recommended in patients with acute non-cardioembolic ischemic stroke or TIA (see *"Interaction with other medicinal products and other forms of interaction"*). 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. Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution (see *Interaction with other medicinal products and other forms of interaction*).

If a patient is to undergo elective surgery and antiplatelet effect is not desired, clopidogrel should be discontinued 5 to 7 days prior to surgery.

Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). Drugs that might induce gastrointestinal lesions (such as acetylsalicylic acid and Non Steroidal Anti-Inflammatory Drugs) should be used with caution in patients taking clopidogrel.

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. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.

The use of clopidogrel 600 mg loading dose is not recommended in patients with non-ST-segment elevation acute coronary syndrome and ≥75 years of age in view of limited data and due to increased bleeding risk in this population.

Due to the limited clinical data in patients ≥ 75 years old with STEMI PCI, and increased risk of bleeding, the use of clopidogrel 600 mg loading dose should be considered only after an individual assessment of the bleeding risk of the patient by the physician.

- ***Recent ischemic stroke***

- Initiation of therapy
  - In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and ASA) should be started no later than 24 hours after the event onset.
  - There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial hemorrhage.
  - Non-Minor IS patients (NIHSS >4)

  In view of the lack of data, use of dual antiplatelet therapy is not recommended (*see Therapeutic Indications*).
- In non-minor IS patients, clopidogrel monotherapy should be started after the first 7 days of the event.

- Recent minor IS or moderate to high-risk TIA in patients for whom intervention is indicated or planned

There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.

In view of the lack of data, clopidogrel cannot be recommended in acute ischemic stroke (less than 7 days)

- ***Thrombotic Thrombocytopenic Purpura (TTP)***

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

- ***Acquired haemophilia***

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

specialists, and clopidogrel should be discontinued.

- ***Cytochrome P450 2C19 (CYP2C19)***

Pharmacogenetics: In patients who are CYP2C19 poor metabolisers clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function (see *Pharmacokinetics properties, Pharmacogenetics*).
Use of drugs that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see *Interaction with other medicinal products and other forms of interaction*).
Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider the use of higher clopidogrel doses in patients who are known CYP2C19 poor metabolisers (see *Pharmacogenetics, Dosage and Administration*).

- ***Cross-reactivity among thienopyridines***

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see *Undesirable effects).* Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for cross-reactivity is advised.

- ***Renal impairment***

Therapeutic experience with clopidogrel is limited in patients with severe renal impairment. Therefore clopidogrel should be used with caution in this population.

- ***Hepatic impairment***

Experience is limited in patients with severe hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

- ***Excipients***

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Oral anticoagulants: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution.

Glycoprotein IIb/IIIa inhibitors: As a pharmacodynamic interaction between clopidogrel and glycoprotein IIb/IIIa inhibitors is possible, concomitant use should be undertaken with caution.

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. As 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 *Special warnings and special precautions for use*). However, clopidogrel and ASA have been administered together for up to one year (see *Pharmacodynamic properties*).

Injectable anticoagulants: 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. As a pharmacodynamic interaction between clopidogrel and heparin is possible, concomitant use should be undertaken with caution.

Drugs associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of drugs associated with bleeding risk should be undertaken with caution (see *"Special warnings and precautions for use"*).
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Thrombolytics: The safety of the concomitant administration of clopidogrel, 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 heparins are co-administered with ASA. (see *Undesirable effects*).

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

Selective Serotonin Reuptake Inhibitors (SSRIs): Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Other concomitant therapy:

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel.

Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see *Special warnings and precautions for use*).

Inhibitors of CYP2C19

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. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole) should be discouraged (see *Precautions and Pharmacokinetics properties, Pharmacogenetics*). If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole**.**

Proton Pump Inhibitors (PPI): In a crossover clinical study, clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 45% (Day 1) and 40% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) with 5 µM ADP was diminished by 39% (24 hours) and 21% (Day 5) when clopidogrel and omeprazole were administered together.

In a second interaction study with omeprazole 80 mg administered 12 hours apart from the clopidogrel standard regimen, the results were similar, indicating that administering clopidogrel and omeprazole at different times does not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19.

In a third interaction study with omeprazole 80 mg administered with a higher dose regimen of clopidogrel (600-mg loading dose followed by 150 mg/day), a degree of interaction was observed similar to that noted in the other omeprazole interaction studies. However, active metabolite formation and platelet aggregation were at the same level as clopidogrel administered alone at the standard dose regimen.

In a crossover clinical study, healthy subjects were administered clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 20% (Day 1) and 14% (Day 5) when clopidogrel and pantoprazole were administered together. Mean inhibition of platelet aggregation was diminished

by 15% (24 hours) and 11% (Day 5) when clopidogrel and pantoprazole were administered together. These results indicate that clopidogrel can be administered with pantoprazole.

The CURRENT trial compared 2 dosing regimens of clopidogrel (600-mg loading dose, then 150 mg/day for 6 days followed by 75 mg/day up to 30 days *vs*. 300-mg loading dose followed by 75 mg/day up to 30 days). A subanalysis (n=18, 432) correlated PPI use (mainly omeprazole and pantoprazole) at randomization and hospital discharge and demonstrated no interaction between clopidogrel and PPI use for the primary endpoint (CV death, MI or stroke) or any secondary endpoints, including stent thrombosis.

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

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

Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, co-administration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis. However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9. It is unlikely that clopidogrel may interfere with the metabolism of drugs such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by cytochrome P4502C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

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

Apart from the specific drug interaction information described above, interaction studies with clopidogrel and some drugs commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medications including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents,

coronary vasodilators, anti-diabetic agents (including insulin), antiepileptic agents, hormone replacement therapy and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

As with other oral P2Y12 inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

Rosuvastatin: Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold (C_{max}) after administration of a 300 mg clopidogrel dose, and by 1.4-fold (AUC) without effect on C_{max} after repeated administration of a 75 mg clopidogrel dose.

4.6 Pregnancy and lactation

- **Pregnancy**

As no clinical data on exposed pregnancies are available, this drug should not be used during pregnancy, unless, in the opinion of the physician, there is a clear need. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see *Preclinical safety data*).

- **Lactation**

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this medicinal product is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to a nursing woman.

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

- **Clinical studies experience:**

Clopidogrel has been evaluated for safety in more than 44,000 patients, including over 12,000 patients treated for 1 year or more. The clinically relevant adverse effects observed in the CAPRIE, CURE, CLARITY, COMMIT, and ACTIVE-A studies are discussed below. Clopidogrel 75 mg/day was well tolerated compared to ASA 325 mg/day in CAPRIE. The overall tolerability of clopidogrel in this study was similar to ASA, regardless of age, gender and ethnicity.

***Haemorrhagic disorders**:*

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 patients that received clopidogrel, gastrointestinal bleeding occurred at a rate of 2.0%, and required hospitalisation in 0.7%. In patients that received ASA, the corresponding rates were 2.7% and 1.1%, respectively.

The overall incidence of other bleedings was higher in patients that received clopidogrel compared to ASA (7.3% *vs.* 6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% *vs.* 0.4%). The most frequently reported events in both treatment groups were: purpura/bruising, and epistaxis. Other less frequently reported events were haematoma, haematuria, and eye bleeding (mainly conjunctival).

The incidence of intracranial bleeding was 0.4% in patients that received clopidogrel and 0.5% for patients that received ASA.

In CURE, the administration of clopidogrel + ASA as compared to placebo + ASA was not associated with a statistically significant increase in life-threatening bleeds (event rates 2.2% *vs*. 1.8%) or fatal bleeds (0.2% *vs*. 0.2%), but the risk of major, minor and other bleedings was significantly higher with clopidogrel + ASA: major bleeds (3.7% clopidogrel + ASA *vs*. 2.7% placebo + ASA), non-life-threatening major bleeds (1.6% clopidogrel + ASA *vs*. 1.0% placebo + ASA), primarily gastrointestinal and at puncture sites, and minor bleeds (5.1% clopidogrel + ASA *vs.* 2.4% placebo + ASA). The incidence of intracranial bleeding was 0.1% in both groups.

The major bleeding event rate for clopidogrel + ASA was dose-dependent on ASA ($<$ 100 mg: 2.6%; 100-200 mg: 3.5%; $>$ 200 mg: 4.9%) as was the major bleeding event rate for placebo + ASA ($<$ 100 mg: 2.0%; 100-200 mg: 2.3%; $>$ 200 mg: 4.0%).

The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months [clopidogrel: 599/6,259 (9.6%); placebo: 413/6,303 (6.6%)], 1-3 months [clopidogrel: 276/6,123 (4.5%); placebo: 144/6,168 (2.3%)], 3-6 months [clopidogrel: 228/6,037 (3.8%); placebo: 99/6,048 (1.6%)], 6-9 months [clopidogrel: 162/5,005 (3.2%); placebo: 74/4,972 (1.5%)], 9-12 months [clopidogrel: 73/3,841 (1.9%); placebo: 40/3,844 (1.0%)].

There was no excess in major bleeds 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% *vs.* 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. The incidence of fatal bleeding (0.8% *vs.* 0.6% in the clopidogrel + ASA and the placebo + ASA groups, respectively) and intracranial hemorrhage (0.5% *vs.* 0.7% in the clopidogrel + ASA and the placebo + ASA groups, respectively) was low and similar in both groups.

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

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

Haematological disorders*:*
In CAPRIE, severe neutropenia ($< 0.45 \times 10^9$/l) was observed in 4 patients (0.04%) that received clopidogrel and 2 patients (0.02%) that received ASA.

Two of the 9,599 patients who received clopidogrel and none of the 9,586 patients who received ASA had neutrophil counts of zero.

One case of aplastic anaemia occurred on clopidogrel treatment.

The incidence of severe thrombocytopenia ($< 80 \times 10^9$/l) was 0.2% on clopidogrel and 0.1% on ASA; very rare cases of platelet count $\leq$ 30 G/L have been reported.

In CURE and CLARITY, the numbers of patients with thrombocytopenia or neutropenia was similar in both groups.

Other clinically relevant adverse drug reactions pooled from CAPRIE, CURE, CLARITY, COMMIT, and ACTIVE-A studies with an incidence > 0.1% as well as all serious and relevant ADR are listed below.

The following CIOMS frequency rating is used, when applicable:
Very common $\geq$ 10%; Common $\geq$ 1 and $<$ 10%; Uncommon $\geq$ 0.1 and $<$ 1%; Rare $\geq$ 0.01 and $<$ 0.1%; Very rare $<$ 0.01%, Unknown (cannot be estimated from available data).

***Central and peripheral nervous system disorders*:**
- Uncommon: Headache, Dizziness and Paraesthesia
- Rare: Vertigo

Gastrointestinal system disorders:
- Common: Dyspepsia, Abdominal pain, Diarrhoea
- Uncommon: Nausea, Gastritis, Flatulence, Constipation, Vomiting, Gastric ulcer and duodenal ulcer

Platelet, bleeding and clotting disorders:
- Uncommon: Bleeding time increased and Platelets decreased

Skin and appendages disorders:
- Uncommon: Rash and Pruritus

White cell and RES disorders:
- Uncommon: Leucopenia, Neutrophils decreased and Eosinophilia

- **Post-marketing experience**

Bleeding is the most common reaction reported in the post-marketing experience and was mostly reported during the first month of treatment.

Bleeding: some cases were reported with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage); serious cases of skin bleeding (purpura), musculo-skeletal bleeding (haemarthrosis, haematoma), eye bleeding (conjunctival, ocular, retinal), epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), haematuria and haemorrhage of operative wound have been reported; cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with acetylsalicylic acid or clopidogrel with acetylsalicylic acid and heparin (see *Special warnings and special precautions for use*).

Frequencies for the following adverse reactions are not known (cannot be estimated form available data).

Blood and the lymphatic system disorders:
- Serious cases of bleeding, mainly skin, musculo-skeletal, eye (conjunctival, ocular, retinal) and respiratory tract bleeding, epistaxis, haematuria and haemorrhage of operative wound; cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage),
- Agranulocytosis, aplastic anaemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired haemophilia A

Cardiac disorders:
- Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel

Immune system disorders:
- Anaphylactoid reactions, Serum sickness

- Cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see *Precautions).*
- Insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)

Psychiatric disorders:
- Confusion, Hallucinations

Nervous system disorders:
- Taste disturbances, ageusia

Vascular disorders:
- Vasculitis, Hypotension

Respiratory, thoracic and mediastinal disorders:
- Bronchospasm, Interstitial Pneumonitis, eosinophilic pneumonia

Gastrointestinal disorders:
- Colitis (including ulcerative or lymphocytic colitis), Pancreatitis, Stomatitis

Hepato-biliary disorders:
- Hepatitis, Acute liver failure

Skin and subcutaneous tissue disorders:
- Maculopapular, erythematous or exfoliative rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis~~)~~, acute generalized exanthematous pustulosis (AGEP)), drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), eczema, lichen planus

Musculoskeletal, connective tissue and bone disorders:
- Arthralgia, Arthritis, Myalgia

Renal and urinary disorders:
- Glomerulopathy

Reproductive systems and breast disorders:
- Gynaecomastia

General disorders and administration site conditions:
- Fever

Investigations:
- Abnormal liver function test, Blood creatinine increase

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
Pharmacotherapeutical group: platelet aggregation inhibitors excl. Heparin, ATC Code: BO1AC/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 P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

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

Repeated doses of 75 mg/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/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 7 double-blind studies involving over 100,000 patients: CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY , COMMIT, CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events) and POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) and ACTIVE-A study (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events), studies comparing clopidogrel to placebo, both drugs 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 ischemic 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 ischemic events (combined end point of myocardial infarction, ischemic 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 1000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischemic 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 (MI, ischemic 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). 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). 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 ischemia. Patients were required to have either ECG changes compatible with new ischemia 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, 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 PTCA with or without stent and 10% when they underwent 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 *Special warnings and special precautions for use*).

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 ischemia) 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 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 ischemia). 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 drugs, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily).

<u>ST-segment Elevation Myocardial Infarction</u>

In patients with acute ST-segment elevation MI (STEMI), safety and efficacy of clopidrogrel have been evaluated in 2 randomised, placebo-controlled, double blind studies, CLARITY ,a prospective subgroup analysis of CLARITY (CLARITY PCI) and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1,752) or placebo (n=1,739), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before coronary angiography, for patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients $\geq$ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta-blockers, 54.7% ACE inhibitors and 63% statins. Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint, representing an absolute reduction of 6.7% and a 36% odds reduction in favor of clopidogrel (95% CI: 24, 47%; $p < 0.001$), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

CLARITY PCI sub-group analysis involved 1,863 STEMI patients undergoing PCI. Patients receiving 300 mg loading dose (LD) of clopidogrel (n=933) had a significant reduction in incidence of cardiovascular death, MI or stroke following PCI compared to those receiving placebo (n=930) (3.6% with clopidogrel pre-treatment versus 6.2% with placebo, OR: 0.54; 95% CI: 0.35-0.85; p=0.008). The patients receiving 300 mg LD of clopidogrel had a significant reduction in incidence of cardiovascular death, MI or stroke through 30 days following PCI compared to those receiving placebo (7.5% with clopidogrel pre-treatment versus 12.0% with placebo, OR: 0.59; 95% CI: 0.43-0.81; p=0.001). However, this composite endpoint when assessed in the overall population of the CLARITY study was not statistically significant as a secondary endpoint. No significant difference was observed in the rates of major or minor bleeding between both the treatments (2.0% with clopidogrel pre-treatment versus 1.9% with placebo, p>0.99). The findings of this analysis support the early use of clopidogrel loading dose in STEMI and the strategy of routine clopidogrel pretreatment in patients undergoing PCI.

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.

Clopidogrel 600 mg Loading Dose in Acute Coronary Syndrome Patients Undergoing PCI

CURRENT-OASIS-7 *(Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events Seventh Organization to Assess Strategies in Ischemic Syndromes)*
This randomized factorial trial included 25,086 individuals with acute coronary syndrome (ACS) intended for early PCI. Patients were randomly assigned to either double-dose (600 mg on Day 1, then 150 mg on Days 2–7, then 75 mg daily) versus standard-dose (300 mg on day 1 then 75 mg daily) clopidogrel, and high-dose (300–325 mg daily) versus low-dose (75–100 mg daily) ASA. The 24,835 enrolled ACS patients underwent coronary angiography and 17,263 received PCI. Among the 17,263 patients receiving PCI treatment, when compared with the standard dose, double-dose clopidogrel reduced the rate of the primary endpoint (3.9% vs 4.5% adjusted HR= 0.86, 95% CI 0.74-0.99, p=0.039) and significantly reduced stent thrombosis (1.6% vs 2.3%, HR: 0.68; 95% CI: 0.55 0.85; p=0.001). Major bleeding was more common with double-dose than with standard-dose clopidogrel (1.6% vs 1.1%, HR=1.41, 95% CI 1.09-1.83, p=0.009). In this trial, clopidogrel 600 mg loading dose has shown consistent efficacy in patients age ≥75 years of age and patients <75 years of age.

ARMYDA-6 MI *(The Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty - Myocardial Infarction)*
This randomized, prospective, international, multicenter trial evaluated pre-treatment with a 600 mg versus 300 mg clopidogrel LD in the setting of urgent PCI for STEMI. Patients received a clopidogrel 600 mg LD (n=103) or clopidogrel 300 mg LD (n=98) prior to PCI, then were prescribed 75 mg/day from the day after PCI up to 1 year. Patients receiving a 600 mg LD of clopidogrel had a significantly reduced infarct size compared to those receiving a 300 mg LD. There was less frequent thrombolysis in MI flow Grade <3 after PCI in 600 mg LD (5.8% versus 16.3%, p=0.031), improved LVEF at discharge (52.1 ±9.5% versus 48.8 ±11.3%, p=0.026), and 30-day major adverse cardiovascular events were fewer (5.8% versus 15%, p=0.049). No increase in bleeding or entry-site complications were observed (secondary endpoints at Day 30).

HORIZONS-AMI *(Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction)*

This post-hoc analysis trial was conducted to evaluate whether a 600 mg clopidogrel LD provides faster and greater inhibition of platelet activation. The analysis examined the impact of a LD of 600 mg compared with 300 mg on 30-day clinical outcomes in 3,311 patients from the main trial (n=1,153; 300 mg LD group; n=2,158; 600 mg LD group) before cardiac catheterization followed by 75 mg/day dose for =6 months post-discharge. The results showed significantly lower 30-day unadjusted rates of mortality (1.9% versus 3.1%, p=0.03), reinfarction (1.3% versus 2.3%, p=0.02), and definite or probable stent thrombosis (1.7% versus 2.8%, p=0.04) with the 600 mg LD without higher bleeding rates. By multivariable analysis, a 600 mg LD was an independent predictor of lower rates of 30-day major adverse cardiac events (HR: 0.72 [95% CI: 0.53–0.98], p=0.04). Major bleeding rate (non-CABG related) was 6.1% in 600 mg LD group and 9.4% in 300 mg LD group (p=0.0005). Minor bleeding rate was 11.3% in 600 mg LD group and 13.8% in 300 mg LD group (p=0.03).

Long Term (12 Months) Treatment with Clopidogrel in STEMI Patients after PCI

CREDO *(Clopidogrel for the Reduction of Adverse Events During Observation)*
This randomized, double-blind, placebo-controlled trial was conducted in the United States and Canada to evaluate the benefit of long-term (12 month) treatment with clopidogrel after PCI. There were 2,116 patients randomized to receive a 300 mg clopidogrel LD (n=1,053) or placebo (n=1,063) 3 to 24 hours before PCI. All patients also received 325 mg of aspirin. Thereafter, all patients received clopidogrel 75 mg/day through Day 28 in both groups. From Day 29 through 12 months, patients in clopidogrel group received 75 mg/day clopidogrel and in control group received placebo. Both groups received ASA throughout the study (81 to 325 mg/day). At 1-year, significant reduction in the combined risk of death, MI or stroke was observed with clopidogrel (26.9% relative reduction, 95% CI: 3.9%-44.4%; p=0.02; absolute reduction 3%) compared to placebo. No significant increase in the rate of major bleeding (8.8% with clopidogrel versus 6.7% with placebo, p=0.07) or minor bleeding (5.3% with clopidogrel versus 5.6% with placebo, p=0.84) at 1-year was observed. The major finding of this study is that continuation of clopidogrel and ASA for at least 1-year leads to a statistically and clinically significant reduction in major thrombotic events.

EXCELLENT *(Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting)*
This prospective, open-label, randomized trial was conducted in Korea to evaluate whether 6-month dual antiplatelet therapy (DAPT) would be noninferior to 12-month DAPT after implantation of drug-eluting stents. The study included 1,443 patients undergoing implantation who were randomized to receive 6-month DAPT (ASA 100–200 mg/day plus clopidogrel 75 mg/day for 6 months and thereafter ASA alone up to 12 months) or 12-month DAPT (ASA 100–200 mg/day plus clopidogrel 75 mg/day for 12 months). No significant difference was observed in the incidence of target vessel failure (composite of cardiac death, MI or target vessel revascularization) which was primary end point between 6-month and 12-month DAPT groups (HR: 1.14; 95% CI: 0.70 1.86; p=0.60). Also, the study showed no significant difference in the safety end

point (composite of death, MI, stroke, stent thrombosis or TIMI major bleeding) between 6-month and 12-month DAPT groups (HR: 1.15; 95% CI: 0.64-2.06; p=0.64). The major finding of this study was that 6-month DAPT was non-inferior to 12-month DAPT in the risk of target vessel failure.

De-escalation of $P2Y_{12}$ Inhibitor Agents in ACS

Switching from a more potent $P2Y_{12}$ receptor inhibitor to clopidogrel in association with aspirin after acute phase in ACS has been evaluated in two randomized investigator-sponsored studies (ISS) – TOPIC and TROPICAL-ACS – with clinical outcome data.

The clinical benefit provided by the more potent $P2Y_{12}$ inhibitors, ticagrelor and prasugrel, in their pivotal studies is related to a significant reduction in recurrent ischemic events (including acute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischemic benefit was consistent throughout the first year, greater reduction in ischemic recurrence after ACS was observed during the initial days following the treatment initiation. In contrast, post-hoc analyses demonstrated statistically significant increases in the bleeding risk with the more potent $P2Y_{12}$ inhibitors, occurring predominantly during the maintenance phase, after the first month post-ACS. TOPIC and TROPICAL-ACS were designed to study how to mitigate the bleeding events while maintaining efficacy.

TOPIC *(Timing Of Platelet Inhibition after acute Coronary syndrome)*

This investigator-sponsored, randomized, open-label trial included ACS patients requiring PCI. Patients on aspirin and a more potent $P2Y_{12}$ blocker and without adverse event at one month were assigned to switch to fixed-dose aspirin plus clopidogrel (de-escalated dual antiplatelet therapy (DAPT)) or continuation of their drug regimen (unchanged DAPT).

Overall, 645 of 646 patients with STEMI or NSTEMI or unstable angina were analyzed (de-escalated DAPT (n=322); unchanged DAPT (n=323)). Follow-up at one year was performed for 316 patients (98.1%) in the de-escalated DAPT group and 318 patients (98.5%) in the unchanged DAPT group. The median follow-up for both groups was 359 days. The characteristics of the studied cohort were similar in the 2 groups.

The primary outcome, a composite of cardiovascular death, stroke, urgent revascularization, and BARC (Bleeding Academic Research Consortium) bleeding ≥2 at 1 year post ACS, occurred in 43 patients (13.4%) in the de-escalated DAPT group and in 85 patients (26.3%) in the unchanged DAPT group (p<0.01). This statistically significant difference was mainly driven by fewer bleeding events, with no difference reported in ischemic endpoints (p=0.36), while BARC ≥2 bleeding occurred less frequently in the de-escalated DAPT group (4.0%) versus 14.9% in the unchanged DAPT group (p<0.01). Bleeding events defined as all BARC occurred in 30 patients

(9.3%) in the de-escalated DAPT group and in 76 patients (23.5%) in the unchanged DAPT group (p<0.01).

TROPICAL-ACS *(Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes)*
The investigator-sponsored, randomized, open-label trial included 2,610 biomarker-positive ACS patients after successful PCI. Patients were randomized to receive either prasugrel 5 or 10 mg/d (Days 0-14) (n=1306), or prasugrel 5 or 10 mg/d (Days 0-7) then de-escalated to clopidogrel 75 mg/d (Days 8-14) (n=1304), in combination with ASA (<100 mg/day). At Day 14, platelet function testing (PFT) was performed. The prasugrel-only patients were continued on prasugrel for 11.5 months.

The de-escalated patients underwent high platelet reactivity (HPR) testing. If HPR≥46 units, the patients were escalated back to prasugrel 5 or 10 mg/d for 11.5 months; if HPR<46 units, the patients continued on clopidogrel 75 mg/d for 11.5 months. Therefore, the guided de-escalation arm had patients on either prasugrel (40%) or clopidogrel (60%). All patients were continued on aspirin and were followed for one year.

The primary endpoint was the combined incidence of CV death, MI, stroke and BARC bleeding grade ≥2 at 12 months. The study met its primary endpoint of showing non-inferiority - 95 patients (7%) in the guided de-escalation group and 118 patients (9%) in the control group (p non-inferiority=0.0004) had an event. The guided de-escalation did not result in an increased combined risk of ischemic events (2.5% in the de-escalation group vs 3.2% in the control group; p non -inferiority=0.0115), nor in the key secondary endpoint of BARC bleeding ≥2 (5% in the de-escalation group versus 6% in the control group (p=0.23)). The cumulative incidence of all bleeding events (BARC class 1 to 5) was 9% (114 events) in the guided de-escalation group versus 11% (137 events) in the control group (p=0.14).

<u>Dual Antiplatelet Therapy (DAPT) in Acute Minor IS or Moderate to High-risk TIA</u>

DAPT with combination clopidogrel and ASA as a treatment to prevent stroke after an acute minor IS or moderate to high-risk TIA has been evaluated in two randomized investigator-sponsored studies (ISS) – CHANCE and POINT – with clinical safety and efficacy outcome data.

CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events)
This randomized, double-blinded, multicenter, placebo-controlled clinical trial included 5,170 Chinese patients with acute TIA (ABCD2 score ≥4) or acute minor stroke (NIHSS ≤3). Patients in both groups received open-label ASA on day 1 (with the dose ranging from 75 to 300 mg, at the discretion of the treating physician). Patients randomly assigned to the clopidogrel–ASA group received a loading dose of 300 mg of clopidogrel on day 1, followed by a dose of 75 mg of clopidogrel per day on days 2 through 90, and ASA at a dose of 75 mg per day on days 2 through 21. Patients

randomly assigned to the ASA group received a placebo version of clopidogrel on days 1 through 90 and ASA at a dose of 75 mg per day on days 2 through 90.

The primary efficacy outcome was any new stroke event (ischemic and hemorrhagic) in the first 90 days after acute minor IS or high-risk TIA. This occurred in 212 patients (8.2%) in the clopidogrel-ASA group compared with 303 patients (11.7%) in the ASA group (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.57 to 0.81; P<0.001). IS occurred in 204 patients (7.9%) in the clopidogrel–ASA group compared with 295 (11.4%) in the ASA group (HR, 0.67; 95% CI, 0.56 to 0.81; P<0.001). Hemorrhagic stroke occurred in 8 patients in each of the two study groups (0.3% of each group). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel–ASA group and in eight (0.3%) in the ASA group (P = 0.73). The rate of any bleeding event was 2.3% in the clopidogrel–ASA group as compared with 1.6% in the ASA group (HR, 1.41; 95% CI, 0.95 to 2.10; P = 0.09).

POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)
This randomized, double-blinded, multicenter, placebo-controlled clinical trial included 4,881 international patients with acute TIA (ABCD2 score ≥4) or minor stroke (NIHSS ≤3). All patients in both groups received open-label ASA on day 1 to 90 (50-325 mg depending upon the discretion of the treating physician). Patients randomly assigned to the clopidogrel group received a loading dose of 600 mg of clopidogrel on day 1, followed by 75 mg of clopidogrel per day on days 2 through 90. Patients randomly assigned to the placebo group received clopidogrel placebo on days 1 through 90.

The primary efficacy outcome was a composite of major ischemic events (IS, MI or death from an ischemic vascular event) at day 90. This occurred in 121 patients (5.0%) receiving clopidogrel plus ASA compared with 160 patients (6.5%) receiving ASA alone (HR, 0.75; 95% CI, 0.59 to 0.95; P = 0.02). The secondary outcome of IS occurred in 112 patients (4.6%) receiving clopidogrel plus ASA compared with 155 patients (6.3%) receiving ASA alone (HR, 0.72; 95% CI, 0.56 to 0.92; P = 0.01). The primary safety outcome of major hemorrhage occurred in 23 of 2,432 patients (0.9%) receiving clopidogrel plus ASA and in 10 of 2,449 patients (0.4%) receiving ASA alone (HR, 2.32; 95% CI, 1.10 to 4.87; P = 0.02). Minor hemorrhage occurred in 40 patients (1.6%) receiving clopidogrel plus ASA and in 13 (0.5%) receiving ASA alone (HR, 3.12; 95% CI, 1.67 to 5.83; P < 0.001).

CHANCE and POINT Time Course Analysis
There was no benefit of continuing DAPT beyond 21 days. The net clinical benefit of continuing DAPT after 3 weeks was not demonstrated. A time-course distribution of major ischemic events and major hemorrhages by treatment assignment was done to analyze the impact of the short-term time-course of DAPT

- **Atrial Fibrillation**

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in

ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

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

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

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

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

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

The number of patients who reached the primary endpoint (time to first occurrence of stroke, MI, non-CNS systemic embolism or vascular death) was 832 (22.1%) in the group treated with clopidogrel + ASA and 924 (24.4%) in the placebo + ASA group

The benefit of clopidogrel + ASA was noted early and was maintained throughout the duration of the study up to 5 years; the rate of primary events was consistently lower in the clopidogrel + ASA group compared with the placebo + ASA group.

The reduction in the risk of major vascular events in the group treated with clopidogrel + ASA was primarily due to a large reduction in the incidence of strokes. Strokes occurred in 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receiving placebo + ASA.

The rate of ischemic stroke was significantly lower in the clopidogrel + ASA group than in the placebo + ASA group (6.2% *vs*. 9.1%; relative risk reduction, 32.4%; 95% CI, 20.2% to 42.7%).

The risk of stroke of any severity was reduced with the use of clopidogrel + ASA. In addition, 46 fewer non-disabling strokes and 69 fewer disabling or fatal strokes were reported with clopidogrel + ASA as compared to placebo + ASA.

There was a trend for reduction in the rates of myocardial infarction in the group treated with clopidogrel + ASA (relative risk reduction, 21.9%; 95% CI, -3% to 40.7%; p=0.08). The rates of non-CNS systemic embolism and death from vascular causes were similar between the two groups.

The effectiveness of clopidogrel + ASA was noted early and was maintained throughout the duration of the study up to 5 years; the rate of stroke was consistently lower in the clopidogrel + ASA group compared with the placebo + ASA group.

Clopidogrel + ASA reduced the total number of hospital days for cardiovascular causes. The total number of days of cardiovascular hospitalizations was 30,276 for clopidogrel + ASA and 34,813 for placebo + ASA.

- **Paediatric Studies**

A randomised, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. In this study, 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomised to receive clopidogrel 0.2 mg/kg/day (n=467) or placebo (n=439) along with concomitant background therapy up to the time of second stage surgery. The mean time between shunt palliation and first administration of study medicinal product was 20 days. Approximately 88% of patients received concomitant ASA (range of 1 to 23 mg/kg/day). There was no significant difference between groups in the primary composite endpoint of death, shunt thrombosis or cardiac related intervention prior to 120 days of age following an event considered of thrombotic nature (89 [19.1%] for the clopidogrel group and 90 [20.5%] for the placebo group) (see *Posology and method of administration*). Bleeding was the most frequently reported adverse reaction in both clopidogrel and placebo groups; however, there was no significant difference in the bleeding rate between groups.

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.

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

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

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

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

Elimination
Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

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

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metaboliser

genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

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

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

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomized, controlled trials. There have been a number of retrospective analyses; however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2,721), CHARISMA (n=2,428), CLARITY-TIMI 28 (n=227) and TRITON-TIMI 38 (n=1,477) as well as a number of published cohort studies.

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

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

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

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

Special populations

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

Gender: In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel *vs*. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Elderly: In elderly (≥ 75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Paediatric patients: No information available.

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.

Renal impairment: After repeated doses of 75 mg clopidogrel per day in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, however, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of clopidogrel per day.

Ethnicity: The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to ethnicity (see *Pharmacokinetics properties, 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 preclinical 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

List of excipients
Excipients: Each tablet contains hydrogenated castor oil, hydroxypropyl cellulose, mannitol E421, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide E172, hypromellose 2910, lactose, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

Incompatibilities
Not applicable

Shelf-life
3 years

Special precautions for storage
Plavix (75 mg): Store between 15°C and 30°C

7. MARKETING AUTHORIZATION HOLDER
Importer: Sanofi-aventis (Thailand) Ltd., Bangkok, Thailand.

8. MARKETING AUTHORIZATION NUMBER
Plavix (75 mg): 1C 156/49 (N)

9. DATE OF AUTHORIZATION
Plavix (75 mg): 28 September 2006

10. DATE OF REVISION OF THE TEXT

Clopidogrel CCDS version 29 (3 June 2021), 30 (24 June 2021), 31 (14 October 2021) and 32 (17 February 2022)