Plavix®
Clopidogrel

SANOFI

COMPOSITION
Plavix 75 mg film-coated tablet
Each film-coated tablet contains 97.875 mg of Clopidogrel hydrogen sulphate form II (molar equivalent of 75 mg of Clopidogrel base).
Plavix 300 mg film-coated tablet
Each film-coated tablet contains 391.5 mg of Clopidogrel hydrogen sulphate form II (molar equivalent of 300 mg of Clopidogrel base).

PHARMACEUTICAL FORM
Plavix 75 mg film-coated tablet
Film-coated tablet: pink, round, biconvex, engraved with <<75>> on one side and <<1171>> on the other side.
Plavix 300 mg film-coated tablet
Film-coated tablet: pink, oblong, engraved with <<300>> on one side and <<1332>> on the other side.

CLINICAL PARTICULARS
Therapeutic indications
Clopidogrel is indicated for the secondary 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 futher information please refer to "*Pharmacodynamic properties*".

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 "*Pharmacodynamic properties*").

- 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 "*Pharmacodynamic properties*").

- Paediatric population
  The safety and efficacy of clopidogrel in children and adolescents under 18 years old have not yet been established.

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

- Hepatic impairment
  Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see "*Special warnings and precautions for use*").

Method of administration.
For oral use.
It may be given or without food.

Contraindications

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

Special warnings and precautions for use

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs). 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.

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with

caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

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

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

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

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

Cytochrome P450 2C19 (CYP2C19)
Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended
doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function.
Tests are available to identify a patient's CYP2C19 genotype.
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.

Cross-reactions among thienopyridines
Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported.
Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-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 signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Renal impairment
Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore
clopidogrel should be used with caution in these patients.

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

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

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

Interaction with other medicinal products and other forms of interaction

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

Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

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. However, clopidogrel and ASA have been administered together for up to one year.
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.

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.

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.

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

Other concomitant therapy: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.
Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

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

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

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.
The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet

aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers (except cimetidine which is a CYP2C19 inhibitor) or antacids interfere with antiplatelet activity of clopidogrel.

Other medicinal products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine.
Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the coadministration of phenobarbital, 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 the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

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

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.

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.

Fertility, pregnancy and lactation

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

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see "*Preclinical safety data*").

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

Fertility
Clopidogrel was not shown to alter fertility in animal studies.

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

Undesirable effects

Summary of the safety profile

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

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

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

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

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the placebo plus ASA group. The incidence of major bleeding was similar between groups . This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups.

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

Tabulated list of adverse reactions

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common (≥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), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Common**	**Uncommon**	**Rare**	**Very Rare, Not Know***
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP), aplastic, anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia,acquired haemophilia, Agranulocytopenia, anaemia
Cardiac Disorders				Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*
Immune system disorders				Serum sickness, anaphylactoid reactions, Cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) Insulin autoimmune syndrome, which can lead to severe

				hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances, ageusia
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity

				syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Reproductive systems and breast disorders			Gynaecomastia	
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

* Information related to clopidogrel with frequency "not known".

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.

PHARMACOLOGICAL PROPERTIES

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 metabolized 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 agonist 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 inhibiton 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 5 double-blind studies involving over 88,000 patients; the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT and ACTIVE-A studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease
The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent MI (<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 1000 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 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 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 1035 (16.5%) in the clopidogrel-treated group and 1187 (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 2172 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=1752) or placebo (n=1739), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients $\geq$ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

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

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

Clopidogrel significantly reduced the relative risk of death from any cause by 7% ($p=0.029$), and the relative risk of the combination of re-infarction, stroke or death by 9% ($p=0.002$), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was

consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

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 ischaemic events (including acute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischaemic benefit was consistent throughout the first year, greater reduction in ischaemic 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 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 ischaemic 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*)
This 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~~1309~~), or prasugrel 5 or 10 mg/d (Days 0-7) then de-escalated to clopidogrel 75 mg/d (Days 8-14) (n=1304~~1309~~), 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 (the combined incidence of CV death, MI, stroke and BARC bleeding grade ≥2 at 12 months) was met showing non-inferiority. Ninety five 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).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Plavix in one or more subsets of the paediatric population for the prevention of thromboembolic events.

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

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

Elimination
Following an oral dose of 14C-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 non functional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patients'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 the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet

aggregation inhibition (5 µM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analysis, however, to evaluate this effect in patient treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1447), and ACTIVE-A (n=601), as well as a number of published cohort studies.

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

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

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

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

Special populations

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

Renal impairment

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

Hepatic impairment

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

Race

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

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.

PHARMACEUTICAL PARTICULARS
List of Excipients
Core: Mannitol (E421), Macrogol 6000, Microcrystalline cellulose, Hydrogenated castor oil, Low substituted hydroxypropylcellulose.
Coating: Hypromellose (E464), Lactose monohydrate, Triacetin (E1518), Titanium dioxide (E171), Red iron oxide (E172).
Polishing agent: Carnauba wax

Incompatibilities
Not applicable.

Shelf-Life
Do not use later than the date of Expiry.

Special precautions for storage
Do not store above 30ºC.

Nature and content of container
Plavix 75 mg film-coated tablet
28, tablets packed in PVC/PVDC/Aluminium blisters or all alumunium blisters in cardboard cartons.
Plavix 300 mg film-coated tablet

10, tablets packed in Aluminium perforated unit-dose blisters in cardboard cartons.

Instructions for use and handling, and disposal (If Appropriate)
Not applicable.

AVAILABILITY
Plavix 75 mg Box of 2 blisters of 14 film coated tablets in packs.
Plavix 300 mg Box of 1 blister of 10 film coated tablets in pack.

HARUS DENGAN RESEP DOKTER

Plavix 75 mg Reg. No. DKL1321205717A1

Manufactured by:
PT Aventis Pharma
Jakarta, Indonesia

Plavix 300 mg Reg. No. DKI1377403617B1

Manufactured by:
Sanofi Winthrop Industrie
1 rue de la Vierge – Ambarès et Lagrave
33565 Carbon Blanc Cedex – France

Registered by:
PT. Aventis Pharma
Jakarta, Indonesia

Under License:
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Date of text revision:
As on approval date

LEAFLET KEMASAN: INFORMASI BAGI PENGGUNA

PLAVIX 75 MG TABLET SALUT SELAPUT
PLAVIX 300 MG TABLET SALUT SELAPUT

Clopidogrel

SANOFI

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai mengkonsumsi obat ini.
- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika ada pertanyaan lebih lanjut, hubungi dokter atau apoteker Anda.
- Obat ini telah diresepkan untuk Anda. Jangan diberikan kepada orang lain. Produk ini dapat berdampak negatif bagi mereka, sekalipun gejala yang Anda dan mereka alami serupa.
- Jika efek sampingnya menjadi serius, atau jika mengalami efek samping yang tidak tercantum dalam leaflet ini, segera konsultasikan kepada dokter atau apoteker Anda.

Informasi dalam lembaran ini:

1. APA ITU PLAVIX DAN TUJUAN PENGGUNAANNYA

Plavix tergolong kelompok obat yang disebut obat antiplatelet. Platelet adalah bagian yang sangat kecil dalam darah yang membentuk gumpalan saat terjadinya pembekuan darah. Dengan mencegah terjadinya gumpalan, obat antiplatelet ini mengurangi resiko pembekuan darah (proses yang disebut trombosis).

Plavix dikonsumsi untuk mencegah pembekuan darah (trombus) yang terbentuk dalam pembuluh darah (arteri) yang mengeras, sebuah proses yang disebut sebagai aterotrombosis, yang dapat menyebabkan sejumlah penyakit aterotrombosis (seperti stroke, serangan jantung, atau kematian).

Anda telah diresepkan Plavix untuk membantu mencegah pembekuan darah dan mengurangi risiko berbahaya seperti itu yang dapat disebabkan karena:
- Pembuluh darah arteri Anda mengalami pengerasan (juga dikenal sebagai aterosklerosis), dan
- Anda pernah mengalami serangan jantung, stroke atau mengalami kondisi yang dikenal sebagai penyakit arteri perifer, atau
- Anda menderita nyeri dada parah yang disebut 'angina tak stabil' atau infark miokard (serangan jantung). Untuk pengobatannya, dokter Anda mungkin telah menempatkan stent dalam arteri yang tersumbat atau menyempit untuk melancarkan aliran darah. Anda juga perlu mendapatkan asam asetilsalisilat (zat yang terkandung dalam obat pereda rasa sakit dan penurun demam serta untuk mencegah pembekuan darah) oleh dokter Anda.

2. SEBELUM ANDA MENGKONSUMSI PLAVIX

Jangan mengkonsumsi Plavix:
- Jika Anda alergi (hipersensitif) terhadap clopidogrel atau bahan lain yang terkandung dalam Plavix;

- Jika Anda mengalami kondisi medis yang saat ini menyebabkan perdarahan seperti ulkus lambung atau pendarahan dalam otak;
- Jika Anda menderita penyakit hati yang berat.

Jika Anda mengalami kondisi tersebut di atas, atau jika Anda ingin memastikan, konsultasikan dengan dokter Anda sebelum mengkonsumsi Plavix.

Hal-hal yang perlu diperhatikan tentang Plavix:
Jika Anda mengalami salah satu kondisi di bawah ini, Anda harus terlebih dahulu memberitahu dokter Anda sebelum mengkonsumsi Plavix:

- jika Anda memiliki resiko pendarahan seperti
  - Kondisi medis yang berisiko perdarahan internal (misalnya ulkus lambung).
  - Kelainan darah yang membuat Anda rentan terhadap perdarahan internal (pendarahan di dalam jaringan, organ atau persendian dalam tubuh Anda).
  - Cedera serius yang belum lama terjadi.
  - Operasi (termasuk gigi) yang belum lama dilakukan.
  - Operasi (termasuk gigi) yang rencananya dilakukan dalam tujuh hari mendatang.
- jika Anda mengalami penyumbatan dalam arteri otak (stroke iskemik) yang terjadi dalam tujuh hari terakhir.
- jika Anda menderita penyakit ginjal atau hati.

Ketika Anda mengkonsumsi Plavix:

- Anda harus memberitahu dokter Anda jika dalam waktu dekat akan menjalani operasi (termasuk gigi).
- Anda juga harus segera memberitahu dokter Anda jika Anda menderita demam dan memar di bawah kulit yang dapat berupa bintik merah, yang dinamakan Thrombotic Thrombocytopenic Purpura atau TTP, dengan ataupun tanpa mengalami kelelahan luar biasa tanpa sebab yang jelas, kebingungan, menguningnya kulit atau mata (sakit kuning) (lihat 'KEMUNGKINAN EFEK SAMPING' bagian 4).
- Jika Anda mengalami cedera atau luka terbuka, pendarahannya dapat berlangsung lebih lama daripada biasanya. Ini terkait dengan cara obat Anda bekerja karena obat tersebut mencegah pembekuan darah. Untuk cedera dan luka ringan seperti tersayat, luka kecil saat mencukur, tidak ada yang perlu dikhawatirkan. Namun, jika Anda cemas dengan pendarahan yang terjadi, segera hubungi dokter Anda (lihat 'KEMUNGKINAN EFEK SAMPING' bagian 4).
- Dokter mungkin merasa Anda perlu menjalani tes darah.

Plavix tidak diperuntukkan untuk anak-anak atau remaja.

Mengkonsumsi obat-obatan lain:
Konsultasikan kepada dokter atau apoteker Anda jika Anda sedang mengkonsumsi atau baru saja minum obat-obatan lain, termasuk obat-obatan yang tidak menggunakan resep dokter.
Beberapa obat tertentu dapat berpengaruh terhadap penggunaan Plavix ataupun sebaliknya.

Secara khusus, Anda harus memberitahu dokter jika Anda sedang mengkonsumsi:

- antikoagulan oral, obat yang mengurangi pembekuan darah,
- obat anti-inflamasi non-steroid, yang lazim digunakan untuk mengobati otot atau persendian yang sakit atau mengalami peradangan,
- Heparin atau obat injeksi lainnya yang digunakan untuk mengurangi pembekuan darah,
- Omeprazol, esomeprazol atau simetidin, obat-obatan untuk mengobati sakit perut,
- Flukonazol, vorikonazol, ciprofloxacin, atau kloramfenikol, obat-obatan untuk mengobati infeksi akibat bakteri dan jamur,
- Fluoxetine, fluvoxamine, atau moclobemide, obat-obatan untuk mengobati depresi,

- Carbamazepine, atau oxcarbazepine, obat-obatan untuk mengobati epilepsi,
- Ticlopidine, zat antiplatelet lainnya.
- Opioid: apabila Anda sedang diobati dengan clopidogrel, Anda harus memberitahu dokter Anda sebelum diresepkan opioid (digunakan untuk mengobati nyeri berat).

Jika Anda menderita nyeri dada yang parah (angina tak stabil atau serangan jantung), dokter Anda mungkin akan meresepkan Plavix dikombinasikan dengan asam asetilsalisilat, zat yang terkandung dalam obat-obatan untuk menghilangkan rasa sakit dan menurunkan demam. Sesekali mengkonsumsi asam asetilsalisilat (tidak lebih dari 1.000 mg dalam kurun waktu 24 jam) pada umumnya tidak menimbulkan masalah, namun jika dikonsumsi untuk waktu yang lama dalam situasi yang berbeda harus terlebih dahulu dikonsultasikan dengan dokter.

Mengkonsumsi Plavix dengan makanan dan minuman
Plavix dapat dikonsumsi dengan ataupun tanpa makanan.

Selama kehamilan atau menyusui
Dianjurkan agar tidak mengkonsumsi produk ini selama kehamilan.
Jika Anda hamil atau mulai merasakan gejala kehamilan, Anda harus terlebih dahulu berkonsultasi dengan dokter atau apoteker Anda sebelum mengkonsumsi Plavix. Jika Anda mulai hamil ketika menjalani pengobatan Plavix, segeralah berkonsultasi ke dokter Anda karena clopidogrel tidak dianjurkan untuk dikonsumsi selama kehamilan.
Jangan menyusui selama mengkonsumsi obat ini.
Jika Anda sedang atau akan menyusui, konsultasikan dengan dokter sebelum mengkonsumsi obat ini.
Mintalah saran dokter atau apoteker Anda sebelum mengkonsumsi obat apapun.

Mengemudi dan mengoperasikan mesin:
Plavix tidak mempengaruhi kemampuan Anda mengemudi atau mengoperasikan suatu mesin.

Informasi penting tentang beberapa bahan Plavix:
Plavix mengandung laktosa. Jika Anda pernah diberitahu oleh dokter Anda bahwa Anda alergi terhadap jenis gula tertentu (misalnya laktosa), konsultasikan terlebih dahulu dengan dokter Anda sebelum mengkonsumsi obat ini.

Plavix juga mengandung castor oil yang terhidrogenasi yang dapat menimbulkan gangguan perut atau diare.

3. CARA MENGKONSUMSI PLAVIX
Saat mengkonsumsi Plavix, lakukanlah tepat seperti anjuran dokter. Tanyakan kepada dokter atau apoteker jika ada hal yang perlu Anda pastikan.
Jika Anda menderita nyeri dada yang parah (angina tidak stabil atau serangan jantung), dokter mungkin memberikan Anda Plavix 300 mg (1 tablet @300 mg atau 4 tablet @75 mg) sekali pada awal pengobatan. Kemudian, dosis normalnya adalah satu tablet Plavix @75 mg per hari untuk diminum dengan atau tanpa makanan, dan pada jam yang sama setiap hari.
Anda harus mengkonsumsi Plavix selama dokter terus meresepkannya untuk Anda.

Jika Anda mengkonsumsi Plavix secara berlebihan:
Hubungi dokter Anda atau rumah sakit terdekat karena risiko pendarahan yang meningkat.

Untuk Plavix 75 mg Tablet Salut Selaput:

Jika Anda lupa mengkonsumsi Plavix:
Jika Anda lupa mengkonsumsi Plavix sesuai jadwal, tetapi menyadarinya dalam kurun waktu 12 jam, segeralah minum obat tersebut. Jadwal berikutnya tetap jatuh pada waktu seperti biasa.
Jika Anda menyadarinya lebih dari 12 jam, minumlah obat berikutnya sesuai jadwal biasanya. Jangan mengkonsumsi dosis ganda untuk menebus dosis yang terlupakan.
Untuk paket berisi 28 tablet, Anda dapat memeriksa hari dimana Anda terakhir mengkonsumsi tablet Plavix dengan melihat kalender yang tertera pada blister.

Jika Anda berhenti mengkonsumsi Plavix:
Jangan menghentikan pengobatan kecuali atas anjuran dokter. Konsultasikan dengan dokter atau apoteker Anda sebelum berhenti.

Untuk pertanyaan lebih lanjut mengenai produk ini, konsultasikan kepada dokter atau apoteker.

4. KEMUNGKINAN EFEK SAMPING
Sebagaimana halnya dengan semua obat-obatan, Plavix dapat menimbulkan efek samping, walaupun tidak semua orang mengalaminya.
Peluang munculnya efek samping yang tercantum di bawah ini dikelompokkan menurut konvensi sebagai berikut:
• sangat umum (terjadi pada lebih dari 1 pengguna dari total 10 orang)
• umum (terjadi pada 1 sampai 10 pengguna dari total 100 orang)
• jarang (terjadi pada 1 sampai 10 pengguna dari total 1.000 orang)
• langka (terjadi pada 1 sampai 10 pengguna dari total 10.000 orang)
• sangat langka (terjadi pada kurang dari 1 pengguna dari total 10.000 orang)
• tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang ada)

Segera hubungi dokter jika Anda mengalami:
- demam, gejala infeksi atau kelelahan ekstrem. Ini dapat disebabkan oleh penurunan beberapa sel darah yang sangat jarang terjadi.
- gejala penyakit hati seperti menguningnya kulit dan/atau mata (penyakit kuning), terlepas dari apakah itu berhubungan dengan perdarahan yang muncul di bawah kulit berupa bintik-bintik merah, dan/atau kebingungan (lihat bagian 2 dari 'Hal-hal yang perlu diperhatikan tentang Plavix') .
- pembengkakan di dalam mulut atau gangguan kulit seperti ruam dan gatal-gatal, lecet pada kulit. Hal tersebut dapat merupakan pertanda reaksi alergi.

Efek samping yang paling umum dilaporkan tentang Plavix adalah pendarahan. Perdarahan dapat terjadi misalnya di dalam lambung atau usus, memar, hematoma (memar atau pendarahan yang tidak lazim di bawah kulit), hidung berdarah, darah dalam urin. Dalam beberapa kasus pernah terjadi pendarahan di mata, di dalam kepala, paru-paru atau persendian.

Jika Anda mengalami perdarahan yang berkepanjangan saat mengkonsumsi Plavix
Jika Anda terluka atau cedera, mungkin pendarahan berlangsung lebih lama dari biasanya. Hal ini terkait dengan cara obat bekerja karena ia mencegah terjadinya pembekuan darah. Untuk cedera atau luka ringan seperti tersayat sedikit, luka ringan saat mencukur, biasanya tidak ada yang perlu dikhawatirkan. Namun, jika Anda cemas dengan pendarahan yang terjadi, segera hubungi dokter (lihat bagian 2 'Hal-hal yang perlu diperhatikan tentang Plavix').

Efek samping lain yang pernah dilaporkan tentang Plavix adalah:
Efek samping yang umum: Diare, nyeri perut, gangguan pencernaan atau perut terasa panas.

Efek samping yang jarang: Sakit kepala, maag, muntah, mual, konstipasi, gas berlebihan dalam perut atau usus, ruam, gatal-gatal, pusing, kesemutan dan mati rasa.
Efek samping yang jarang: Vertigo.
Efek samping yang sangat jarang: Penyakit kuning, sakit perut yang parah dengan atau tanpa nyeri punggung, demam, kesulitan bernapas kadang-kadang disertai batuk, reaksi alergi umum, pembengkakan di mulut, kulit melepuh, alergi kulit, peradangan pada mulut (stomatitis); penurunan tekanan darah, kebingungan, halusinasi, nyeri sendi, nyeri otot, perubahan rasa dalam lidah.
Selain itu, dokter Anda mungkin menemukan perubahan dalam darah atau hasil tes urin.
Efek samping yang tidak diketahui: gejala gula darah rendah persisten (terus menerus).

Jika mengalami efek samping yang serius atau mengalami efek samping apapun yang tidak tercantum dalam leaflet ini, hubungi dokter atau apoteker Anda.

5. CARA MENYIMPAN PLAVIX
Jauhkan dari jangkauan dan penglihatan anak-anak.
Jangan mengkonsumsi Plavix setelah tanggal kadaluwarsa yang tertera pada karton dan blister, setelah masa kadaluwarsa.
Ikuti petunjuk pada kemasan tentang aturan penyimpanan.
Simpan pada suhu di bawah 30ºC.
Jangan mengkonsumsi Plavix jika ada tanda-tanda kerusakan.
Obat tidak boleh dibuang melalui limbah air atau limbah rumah tangga. Tanyakan apoteker bagaimana membuang obat-obatan yang tidak diperlukan lagi. Langkah-langkah ini bermanfaat dalam menjaga kelestarian lingkungan.

6. INFORMASI LEBIH LANJUT

Apa yang terkandung dalam Plavix
Zat aktif di dalamnya adalah clopidogrel.
Plavix 75 mg Tablet Salut Selaput
Tiap tablet bersalut selaput ini mengandung 75 mg clopidogrel (sebagai sulfat hidrogen).
Plavix 300 mg Tablet Salut Selaput
Tiap tablet bersalut selaput ini mengandung 300 mg clopidogrel (sebagai sulfat hidrogen).

Bahan lainnya adalah:
- Inti Tablet: manitol (E421), castor oil yang telah dihidrogenasi, mikrokristalin selulosa, macrogol 6000 dan hidroksipropilselulosa substitusi rendah.
- Lapisan tablet: laktosa monohidrat (gula susu), hypromellose (E464), triasetin (E1518), oksida merah besi (E172) dan titanium dioksida (E171),
- Agen Poles: carnauba wax.

Ciri-ciri Plavix dan isi dalam kemasan
Plavix 75 mg Tablet Salut Selaput
Plavix 75 mg tablet salut selaput berbentuk bulat, cembung di kedua sisinya, berwarna merah muda, di satu sisi terukir nomor '75' dan di sisi lain dengan nomor '1171'. Plavix tersedia dalam kemasan karton berisi 28 tablet, dalam blister yang berbahan PVC/PVDC/Aluminium atau yang seluruhnya berbahan aluminium.
Plavix 300 mg Tablet Salut Selaput
Plavix 300 mg tablet salut selaput berbentuk memanjang, berwarna merah muda, terukir di satu sisi dengan nomor '300' dan di sisi lain dengan nomor '1332'. Plavix tersedia dalam kemasan karton berisi 10 tablet, dan tiap tabletnya disimpan dalam blister yang seluruhnya berbahan aluminium dan dilengkapi dengan garis-garis berlubang.

HARUS DENGAN RESEP DOKTER
Plavix 75 mg Reg. No. DKL1321205717A1
Diproduksi oleh:
PT. Aventis Pharma
Jakarta, Indonesia

Plavix 300 mg Reg. No. DKI1377403617B1
Diproduksi oleh:
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1 rue de la Vierge - Ambares et Lagrave
33565 Carbon Blanc Cedex - Perancis

Didaftarkan oleh:
PT. Aventis Pharma
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Tanggal revisi teks:
Sesuai persetujuan