RANCANGAN LEAFLET

CoPlavix®

Clopidogrel / Acetylsalicylic acid (ASA)

SANOFI

COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 100 mg of acetylsalicylic acid (ASA).

PHARMACEUTICAL FORM

Enteric Coated Tablet (tablet).
Light pink, oval, slightly biconvex, engraved with «C75» on one side and «A100» on the other side.

CLINICAL PARTICULARS

Therapeutic indications

CoPlavix is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). CoPlavix is a fixed-dose combination medicinal product for continuation of therapy in:

- 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
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy

For futher information please refer to "*Pharmacodynamic properties*".

Posology and method of administration

Posology
Adults and elderly
CoPlavix should be given as a single daily 75 mg/100 mg dose.

CoPlavix is used following initiation of therapy with clopidogrel and ASA given separately.

- In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section *Pharmacodynamic properties*). If the use of CoPlavix is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.
- In patients with ST segment elevation acute myocardial infarction: Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section *Pharmacodynamic properties*). If the use of CoPlavix is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
- For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

Paediatric population
The safety and efficacy of CoPlavix in children and adolescents under 18 years old have not been established. CoPlavix is not recommended in this population.

Renal impairment
CoPlavix must not be used in patients with severe renal impairment (see section *Contraindications*). Therapeutic experience is limited in patients with mild to moderate renal impairment (see section *Special warnings and precautions for use*). Therefore CoPlavix should be used with caution in these patients.

Hepatic impairment
CoPlavix must not be used in patients with severe hepatic impairment (see section *Contraindications*). Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section *Special warnings and precautions for use)*. Therefore CoPlavix should be used with caution in these patients.

Method of administration
For oral use.
It is recommended to administered under fasting.

Contraindications
Due to the presence of both components of the medicinal product, CoPlavix is contraindicated in case of:
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

In addition, due to the presence of ASA, its use is also contraindicated in:
- Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).
- Severe renal impairment (creatinine clearance <30 ml/min).
- Third trimester of pregnancy (see section *Fertility, pregnancy and lactation*).

Special warnings and precautions for use
Bleeding and haematological disorders
Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section *Undesirable effects*). As a dual antiplatelet agent, CoPlavix 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 other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), CYP2C19 strong inducers, thrombolytics or other medicinal

products associated with bleeding risk such as pentoxifylline (see section *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. The concomitant administration of CoPlavix with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section *Interaction with other medicinal products and other forms of interaction*).

Patients should inform physicians and dentists that they are taking CoPlavix before any surgery is scheduled and before any new medicinal product is taken. Where elective surgery is being considered, the need for dual antiplatelet therapy should be reviewed and consideration given to the use of a single antiplatelet agent. If patients must temporarily stop antiplatelet therapy, CoPlavix should be discontinued 7 days prior to surgery.

CoPlavix 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 also be told that it might take longer than usual to stop bleeding when they take CoPlavix, 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 transient ischaemic attack or stroke
In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of ASA and clopidogrel has been shown to increase major bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

Cytochrome P450 2C19 (CYP2C19)
Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

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

Use of medicinal products 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 section *Interaction with other medicinal products and other forms of interaction*).

CYP2C8 substrates
Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section *Interaction with other medicinal products and other forms of interaction*).

Cross-reactions among thienopyridines
Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section *Undesirable effects*). 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.

Caution required due to ASA
- In patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions.
- In patients with gout since low doses of ASA increase urate concentrations.
- In children under 18 years of age, there is a possible association between ASA and Reye's syndrome. Reye's syndrome is a very rare disease which can be fatal.
- This medicinal product must be administered under close medical supervision in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of haemolysis (see section *Undesirable effects*).
- Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Patients should be counseled about the risks of gastrointestinal injury and bleeding while taking clopidogrel plus ASA with alcohol, especially if alcohol consumption is chronic or heavy.

Gastrointestinal (GI)
CoPlavix should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper GI symptoms as this may be due to gastric ulceration which may lead to gastric bleeding. GI undesirable effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Minor GI symptoms, such as dyspepsia, are common and can occur anytime during therapy. Physicians should remain alert for signs of GI ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about the signs and symptoms of GI undesirable effects and what steps to take if they occur. (See section *Undesirable effects*). In patients concomitantly receiving nicorandil and NSAIDs including ASA and LAS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

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

This medicinal product also 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 CoPlavix with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section *Special warnings and precautions for use*). 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
CoPlavix should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section *Special warnings and precautions for use*).

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 CoPlavix and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section *Special warnings and precautions for use*).

Thrombolytics
The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section *Undesirable effects*). The safety of the concomitant administration of CoPlavix with other thrombolytic agents has not been formally established and should be undertaken with caution (see section *Special warnings and precautions for use*).

NSAIDs
In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs including Cox-2 inhibitors is not recommended (see section *Special warnings and precautions for use*).
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section *Pharmacodynamic properties*).

Metamizole

Metamizole may reduce the effect of ASA on platelet aggregation when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose ASA for cardioprotection .

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 with clopidogrel
Inducers of CYP2C19
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products 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 to both an increase 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 section *Special warnings and precautions for use*).

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

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

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

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

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 (PK) interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

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

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

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

Other concomitant therapy with ASA
Interactions with the following medicinal products have been reported with ASA:

Uricosurics (benzbromarone, probenecid, sulfinpyrazone)
Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Methotrexate
Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with CoPlavix as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Tenofovir
Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

Valproic acid
The concomitant administration of salicylates and valproic acid may result in decreased valproic acid protein binding and inhibition of valproic acid metabolism resulting in increased serum levels of total and free valproic acid.

Varicella vaccine
It is recommended that patients not be given salicylates for an interval of six weeks after receiving the varicella vaccine. Cases of Reye's syndrome have occurred following the use of salicylates during varicella infections.

Acetazolamide
Caution is recommended when co-administering salicylates with acetazolamide as there is an increased risk of metabolic acidosis.

Nicorandil
In patients concomitantly receiving nicorandil and NSAIDs including ASA and LAS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

Alcohol
Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Patients should be counseled about the risks of gastrointestinal injury and bleeding while taking clopidogrel plus ASA with alcohol, especially if alcohol consumption is chronic or heavy.

Other interactions with ASA
Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycemic agents.

Other interactions with clopidogrel and ASA
More than 30,000 patients entered into clinical trials with clopidogrel plus ASA at maintenance doses lower than or equal to 325 mg, and received a variety of concomitant medicinal products including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicinal product interaction information described above, interaction studies with CoPlavix and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed.

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
No clinical data on exposure to CoPlavix during pregnancy are available. CoPlavix should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel/ASA.

Due to the presence of ASA, CoPlavix is contraindicated during the third trimester of pregnancy.

Clopidogrel:
As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section *Preclinical safety data*).

ASA:
Low doses (up to 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.
Doses of 100-500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in reproductive toxicity (see section *Preclinical safety data*). Until the 24th amenorrhea week (5th month of pregnancy), acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or until the 24th amenorrhea week (5th month of pregnancy), the dose should be kept as low and duration of treatment as short as possible.

From the beginning of the sixth month of pregnancy, all prostaglandin synthesis inhibitors may expose:
• the foetus to:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
  - renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
• the mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

Breast-feeding
It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. ASA is known to be excreted in limited amounts in human milk. Breast-feeding should be discontinued during treatment with Coplavix.

Fertility
There are no fertility data with CoPlavix. Clopidogrel was not shown to alter fertility in animal studies. It is unknown whether ASA dose in CoPlavix alters fertility.

Effects on ability to drive and use machines
CoPlavix 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 42,000 patients who have participated in clinical studies, including over 30,000 patients treated with clopidogrel plus ASA, and over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in four major

studies, the CAPRIE study (a study comparing clopidogrel alone to ASA) and the CURE, CLARITY and COMMIT studies (studies comparing clopidogrel plus ASA to ASA alone) are discussed below. Overall clopidogrel 75 mg/day was similar to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in the 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 group taking ASA alone. 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.

Tabulated list of adverse reactions

Adverse reactions that occurred with clopidogrel alone, with ASA alone or with clopidogrel in combination with ASA 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 known
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP), bone marrow failure*, aplastic anaemia, pancytopenia, bicytopenia*, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia, haemolytic

				anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency*
Cardiac disorders				Kounis syndrome (vasospastic allergic angina/ allergic myocardial infraction) in the context of a hypersensitivity reaction due to acetylsalicylic acid* or clopidogrel**
Immune system disorders				Anaphylactic shock*, Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section *Special warnings and precautions for use*)**, insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)**, aggravation of allergic symptoms of food allergy*
Metabolism and nutrition disorders				Hypoglycaemia*, gout* (see section *Special warnings and precautions for use*)
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal		Taste disturbances, ageusia

		outcome, especially in elderly), headache, paraesthesia, dizziness		
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	Hearing loss* or tinnitus*
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis (including Henoch-Schonlein purpura*), hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, non-cardiogenic pulmonary edema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid*, 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. Upper gastrointestinal disorders (oesophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis; gastro-duodenal ulcer/perforations)*; lower gastrointestinal

				disorders (small [jejunum and ileum] and large [colon and rectum] intestinal ulcers, colitis and intestinal perforation)*; upper gastro-intestinal symptoms* such as gastralgia (see section *Special warnings and precautions for use*); these ASA-related GI reactions may or may not be associated with haemorrhage, and may occur at any dose of acetylsalicylic acid and in patients with or without warning symptoms or a previous history of serious GI events*. Colitis (including ulcerative or lymphocytic colitis), stomatitis, acute pancreatitis in the context of a hypersensitivity reaction due to acetylsalicylic acid*
Hepato-biliary disorders				Acute liver failure, liver injury, mainly hepatocellular*, hepatitis, elevation of hepatic enzymes*, abnormal liver function test, chronic hepatitis*
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme) acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-

				induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus, fixed eruption*
Reproductive systems and breast disorders			Gynecomastia	
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Renal failure*, acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)*, glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever, edema*
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

* Information reported in published information for ASA with frequency "not known".
** Information related to clopidogrel with frequency "not known".

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Overdose

Clopidogrel

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.

ASA

The following symptoms are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis occurs as a result of a suppressive effect on the respiratory centre. A metabolic acidosis also arises due to the presence of salicylates. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage.

The following symptoms can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of acetylsalicylic acid is 25-30 g. Plasma salicylate concentrations above 300 mg/l (1.67 mmol/l) suggest intoxication.

Overdose with ASA/ clopidogrel fixed dose combination may be associated with increased bleeding and subsequent bleeding complications due to the pharmacological activity of clopidogrel and ASA.

Non-cardiogenic pulmonary edema can occur with acute and chronic acetylsalicylic acid overdose (see section *Undesirable effects*).

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excl. Heparin, ATC Code: B01AC30.

Mechanism of action

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

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

Pharmacodynamic effects
Repeated doses of clopidogrel 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.

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Clinical efficacy and safety
The safety and efficacy of clopidogrel plus ASA have been evaluated in three double-blind studies involving over 61,900 patients: the CURE, CLARITY and COMMIT studies, comparing clopidogrel plus ASA to ASA alone, both treatments given in combination with other standard therapy.

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) plus ASA (75-325 mg once daily) or ASA alone (N=6,303), (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 plus ASA and ASA alone 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 plus ASA group and 719 (11.4%) in the ASA group, a 20% relative risk reduction (RRR) (95% CI of 10%-28%; p=0.00009) for the clopidogrel plus ASA group [17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)]. New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the

clopidogrel plus ASA group was not further increased, whereas the risk of haemorrhage persisted (see section *Special warnings and precautions for use*).

The use of clopidogrel in CURE was associated with a decrease in the need for thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).
Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

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month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel plus ASA group was not further increased, whereas the risk of haemorrhage persisted (see section *Special warnings and precautions for use*).

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The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel plus ASA group and 1,187 (18.8%) in the ASA group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the clopidogrel plus ASA group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel plus ASA group and 363 (5.8%) in the ASA group]. There was no observed effect on the rate of rehospitalisation for unstable angina.
The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

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

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

Fifteen percent (15.0%) of patients in the clopidogrel plus ASA group and 21.7% in the group treated with ASA alone 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) plus ASA (162 mg/day), or ASA alone (162 mg/day) (n=22,891), 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 plus ASA 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 P2Y12 Inhibitor Agents in ACS

Switching from a more potent P2Y12 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 P2Y12 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 P2Y12 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 P2Y12 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), 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 (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 waived the obligation to submit the results of studies with CoPlavix in all subsets of the paediatric population in the treatment of coronary atherosclerosis (see section *Posology and method of administration* for information on paediatric use).

Pharmacokinetic properties
Absorption
1) Bioequivalency study
The of plasma concentration profile of clopidogrel and aspirin after 1 tablet of clopidogrel hydrogen sulfate/aspirin combination tablet or 1 tablet of each single entity tablet (75 mg clopidogrel and 100 mg aspirin) concomitantly administered in fasted 55 healthy Japanese male subjects by cross-over design.

Pharmacokinetic parameters after a single oral dose clopidogrel hydrogen sulfate/aspirin combination drug			C_{max} (ng/mL)	Tmax (h)*	AUC_{0-t} (ng・h/mL) **	$t_{1/2}$ (h)
coplavix	clopidogrel	clopidogrel	2.12 ± 3.00	0.75	2.59± 3.19	4.53 ± 3.18
		active metabolite H4	8.92 ± 5.11	0.75	8.83 ± 4.69	0.460 ± 0.219
	aspirin	aspirin	809 ± 445	5.50	1070 ± 357	0.437 ± 0.152
		salicylic acid	4820 ± 1410	6.50	24700 ± 6540	2.25 ± 0.625
C + A	clopidogrel	clopidogrel	1.98 ± 2.75	0.75	2.8873.86	5.29 ± 4.28
		active metabolite H4	8.93 ± 4.52	0.75	9.22 ± 4.54	0.438 ± 0.159
	aspirin	aspirin	853 ± 417	4.50	1040 ± 366	0.391 ± 0.0877
		salicylic acid	5150 ± 1450	6.00	25300 ± 6560	2.28 ± 0.676

(mean±S.D.)
*:Median
**:clopidogrel: 0 – 24hour, active metabolite H4: 0 – 4hour, aspirin and slicirate: 0 – 16hour

Pharmacokinetic parameters of aspirin

	C_{max} (ng/mL)	Tmax (h)*	AUC $_{0\text{-}16}$(ng・h/mL)	$t_{1/2}$ (h)
ComPlavin	821 ± 365	5.00	1090 ± 352	0.495± 0.236
C+A	750 ± 355	4.75	961 ± 304	0.471 ± 0.496

(mean±S.D.)

*: Median

2) Effect of Food

The of plasma concentration profile of clopidogrel and aspirin after 1 tablet of clopidogrel hydrogen sulfate/aspirin combination tablet after taking food or in fasted1 in fasted 18 healthy Japanese male subjects by cross-over design are shown below.

		C_{max} (ng/mL)	Tmax (h)*	AUC (ng・h/mL) **
Clopidogrel hydrogen sulfate	fasted	1.39±1.66	0.75	1.84± 2.09
	After taking food	1.08± 0.54	2.50	2.62 ± 1.31
Aspirin	fasted	727± 483	4.50	809 ± 411
	After taking food	1010 ± 372	5.50	1050 ± 275

*: mean±S.D

**: Median

Metabolism

1) Clopidogrel

After absorption, clopidogrel hydrogen sulfate is mainly metabolized by two pathways: 1) formation of the inactive metabolite SR26334 (main metabolite) by esterase and 2) formation of the oxidative metabolite via the drug metabolic enzyme cytochrome P450 (CYP). The active metabolite H4 is formed via the latter pathway.

The CYP isozyme related to the formation of H4 are mainly CYP3A4, CYP1A2, CYP2C19 and CYP2B6[7,8)]

(*in vitro*). SR26334 inhibits CYP2C9 (*in vitro*)[9)]

2) Aspirin

Aspirin is hydrolyzed to salicylic acid during absorption from intestine and in many tissues(mainly in liver). Salicylic acid is transformed to glycine conjugated and glucroninzed. And small fraction is oxidized to gentisic acid.

Distribution

1) Clopidogrel

Reference (Studies of laboratory animals)

When 14C-4-clopidogrel hydrogen sulfate (5.0 mg/kg as clopidogrel) was administered orally to rats at a single dose, the peak level of radioactivity was seen at 0.25 – 2 hr after administration in

most of organs. The radioactivity was highest in the gut wall and liver, with little distribution in the brain, spinal cord and skeletal muscle[10]. Repeated administration did not cause accumulation of the drug in the organs examined[11].

2) Aspirin
Salicylic acid, metabolite of aspirin, is distributed throughout the most body tissues.

Excretion

1) Clopidogrel
Reference (overseas data)
When ^{14}C4-clopidogrel hydrogen sulfate (75 mg as clopidogrel) was administered to healthy volunteers as a single oral dose, the cumulative excretion radioactivity in 5 days was approximately 92% of administrated radioactivity; about 41% was excreted in the urine and about 51% was excreted in the faeces[12].

2) Aspirin
Aspirin is excreted in the urine as salicylic acid and its conjugate.

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

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 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 analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1477), and ACTIVE-A (n=601), as well as a number of published cohort studies.

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

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

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

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

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

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

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

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

<u>Acetylsalicylic acid (ASA):</u>
Absorption
Following absorption, the ASA in CoPlavix is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of ASA are essentially undetectable 1.5-3 hours after dosing.

Distribution

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (<100 micrograms/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

Biotransformation and Elimination
The ASA in CoPlavix is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in CoPlavix has a plasma half-life of approximately 2 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10−20 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged active substance depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% phenolic- and 5% acyl-glucuronides of salicylic acid.
Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant PK interactions are unlikely

Preclinical safety data
Clopidogrel
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.

Acetylsalicylic acid
Single-dose studies have shown that the oral toxicity of ASA is low. Repeat-dose toxicity studies have shown that levels up to 200 mg/kg/day are well tolerated in rats; dogs appear to be more

sensitive, probably due to the high sensitivity of canines to the ulcerogenic effects of NSAIDs. No genotoxicity or clastogenicity issues of concern have been found with ASA. Although no formal carcinogenicity studies have been performed with ASA, it has been shown that it is not a tumour promoter.

Reproduction toxicity data show that ASA is teratogenic in several laboratory animals.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

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
CoPlavix 75/100 mg film coated tablet
30, tablets packed Aluminium blisters in cardboard cartons.

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

AVAILABILITY
CoPlavix 75/100 mg Box of 3 blisters of 10 film coated tablets in packs.

HARUS DENGAN RESEP DOKTER

CoPlavix 75/100 mg Reg. No. DKI1977404315A1

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

Date of text Revision
As on approval date

LEAFLET KEMASAN: INFORMASI BAGI PENGGUNA

Coplavix 75 mg/100 mg enteric coated tablets
Clopidogrel /Acetylsalicylic acid

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 COPLAVIX DAN TUJUAN PENGGUNAANNYA

Coplavix mengadung Clopidogrel dan Acetylsalicylic acid (ASA) dan 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).

Coplavix 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 Coplavix 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 COPLAVIX

Jangan mengkonsumsi Coplavix:
- Jika Anda alergi (hipersensitif) terhadap clopidogrel, Asam Asetilsalisilat atau bahan lain yang terkandung dalam Coplavix;

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- Jika kamu alergi produk lain yang disebut produk non-steroidal anti-inflammatory yang biasanya digunakan untuk mengobati rasa sakit dan atau kondisi inflamasi pada otot
- 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 memiliki kondisi asma
- Jika Anda menderita penyakit ginjal yang berat
- Jika Anda sedang hamil trimester terakhir

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

Hal-hal yang perlu diperhatikan tentang Coplavix:

Jika Anda mengalami salah satu kondisi di bawah ini, Anda harus terlebih dahulu memberitahu dokter Anda sebelum mengkonsumsi Coplavix:

- 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.
- Jika Anda menderita asam urat
- Jika Anda meminum minuman beralkohol karena dapat mengakibatkan terjadinya peningkatan risiko pendarahan atau kerusakan lambung.
- Jika Anda memiliki kondisi yang dikenal penurunan *glucose-6-phosphate dehydrogenase* (G6PD) karena berisiko anemia (kekurangan jumlah sel darah merah)
- JIka Anda memiliki riwayat asma atau reaksi allergi termasuk allergi terhadap obat yang digunakan

Ketika Anda mengkonsumsi Coplavix:

- Anda harus memberitahu dokter Anda jika dalam waktu dekat akan menjalani operasi (termasuk gigi).
- Jika Anda mengalami nyeri pada lambung atau perut atau pendarahan pada lambung atau usus (feses merah atau feses hitam).
- 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.

Coplavix tidak diperuntukkan untuk anak-anak atau remaja kurang dari 18 tahun. Terdapat kaitan antara Acetylsalicylic Acid and *Reye's syndrome* ketika produk yang mengandung Acetylsalicylic Acid diberikan

terhadap anak atau remaja dengan infeksi virus. *Reye's syndrome* merupakan penyakit yang jarang dan dapat menjadi fatal.

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 Coplavix ataupun sebaliknya.

Secara khusus, Anda harus memberitahu dokter jika Anda sedang mengkonsumsi:
- Obat yang dapat meningkatkan risiko pendarahan, seperti
  - 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,
  - ticlopidine, other antiplatelet agent,
  - inhibitor reuptake serotonin selektif (termasuk tetapi tidak terbatas pada fluoxetine atau fluvoxamine), obat-obatan yang biasanya digunakan untuk mengobati depresi
- Rifampicin (digunakan untuk mengobati infeksi berat).
- Omeprazol, esomeprazol, obat-obatan untuk mengobati sakit perut,
- methothrexate, obat yang digunakan untuk mengobati penyakit sendi yang parah (rheumatoid arthritis) atau penyakit kulit (psoriasis),
- acetazolamide, obat yang digunakan untuk mengobati glaukoma (peningkatan tekanan okular) atau epilepsi atau untuk meningkatkan aliran urin
- probenecid, benzbromarone, atau sulfinpyrazone, obat-obatan yang digunakan untuk mengobati gout
- Flukonazol, vorikonazol, obat-obatan untuk mengobati infeksi akibat bakteri dan jamur,
- efavirenz atau tenofovir, obat-obatan untuk mengobati infeksi HIV
- asam valproat, valproat atau karbamazepin, obat-obatan untuk mengobati epilepsi,
- vaksin varicella, obat yang digunakan untuk mencegah cacar air atau herpes zoster, dalam waktu 6 minggu setelah mengonsumsi Coplavix, atau jika Anda menderita infeksi cacar air atau herpes zoster (lihat bagian 2 'Anak-anak dan remaja'),
- moclobemide, obat untuk mengobati depresi,
- repaglinide, obat untuk mengobati diabetes,
- paklitaksel, obat untuk mengobati kanker,
- nikorandil, obat untuk mengobati nyeri dada karena penyakit jantung.
- 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 Coplavix 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.

Selama kehamilan atau menyusui
Jangan gunakan Coplavix selama trimester terakhir kehamilan. Dianjurkan untuk tidak menggunakan obat ini pada trimester pertama dan kedua kehamilan.

Jika Anda hamil atau mulai merasakan gejala kehamilan, Anda harus terlebih dahulu berkonsultasi dengan dokter atau apoteker Anda sebelum mengkonsumsi Coplavix. Jika Anda mulai hamil ketika menjalani pengobatan Coplavix, segeralah berkonsultasi ke dokter Anda karena clopidogrel tidak dianjurkan untuk dikonsumsi selama kehamilan.

Jika Anda menderita nyeri dada yang parah (angina tak stabil atau serangan jantung), dokter Anda mungkin akan meresepkan Coplavix 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 Coplavix dengan makanan dan minuman
Coplavix direkomendasikan untuk diberikan pada saat puasa.

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 Coplavix. Jika Anda mulai hamil ketika menjalani pengobatan Coplavix, 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:
Coplavix tidak mempengaruhi kemampuan Anda mengemudi atau mengoperasikan suatu mesin.

Informasi penting tentang beberapa bahan Coplavix:
Coplavix 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.

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

3. CARA MENGKONSUMSI COPLAVIX
Saat mengkonsumsi Coplavix, 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 Coplavix @75 mg per hari untuk diminum dengan atau tanpa makanan, dan pada jam yang sama setiap hari.
Anda harus mengkonsumsi Coplavix selama dokter terus meresepkannya untuk Anda.

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

Jika Anda lupa mengkonsumsi Coplavix:

Jika Anda lupa mengkonsumsi Coplavix 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 14, 28 dan 84 tablet, Anda dapat memeriksa hari dimana Anda terakhir mengkonsumsi tablet Coplavix dengan melihat kalender yang tertera pada blister.

Jika Anda berhenti mengkonsumsi Coplavix:
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, Coplavix dapat menimbulkan efek samping, walaupun tidak semua orang mengalaminya.

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 Coplavix') .
- 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 Coplavix 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 Coplavix
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 Coplavix').

Efek samping lain yang pernah dilaporkan tentang Coplavix adalah:
Efek samping yang umum (dapat terjadi pada hingga 1 dari 10 orang):
Diare, nyeri perut, gangguan pencernaan atau perut terasa panas.

Efek samping yang ~~jarang~~ tidak umum (dapat terjadi pada hingga 1 dari 100 orang):
Sakit kepala, maag, muntah, mual, konstipasi, gas berlebihan dalam perut atau usus, ruam, gatal-gatal, pusing, kesemutan dan mati rasa.

Efek samping yang jarang (dapat terjadi pada hingga 1 dari 1000 orang):
Vertigo, enlarged breasts in males. pembesaran payudara pada pria.

Efek samping yang sangat jarang (dapat terjadi pada hingga 1 dari 10.000 orang):
Penyakit kuning, rasa terbakar di perut dan / atau kerongkongan; sakit perut yang parah dengan atau tanpa nyeri punggung, demam, kesulitan bernapas kadang-kadang disertai batuk, reaksi alergi umum (seperti, sensasi panas dengan rasa tidak nyaman yang umum yang tiba-tiba sampai pingsan), pembengkakan di mulut, kulit melepuh, alergi kulit, peradangan pada mulut (stomatitis); penurunan tekanan darah, kebingungan, halusinasi, nyeri sendi, nyeri otot, perubahan rasa dalam lidah, inflammation of small vessels (radang pembuluh kecil)

Efek samping dengan frekuensi kejadian tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang ada)
Perforasi ulkus, dering di telinga, gangguan pendengaran, reaksi alergi atau hipersensitifitas yang mengancam jiwa dengan nyeri dada atau perut, penyakit ginjal, gula darah rendah, gout (kondisi nyeri, sendi bengkak yang disebabkan oleh kristal asam urat) dan alergi makanan yang memburuk, anemia (jumlah rendah sel darah merah) (lihat bagian 2 SEBELUM ANDA MENGKONSUMSI COPLAVIX), bengkak.

Selain itu, dokter Anda mungkin menemukan perubahan dalam darah atau hasil tes urin.
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 COPLAVIX
Jauhkan dari jangkauan dan penglihatan anak-anak.
Jangan mengkonsumsi Coplavix setelah tanggal kadaluwarsa yang tertera pada karton dan blister, setelah EXP. Tanggal kadaluarsa merujuk pada hari terakhir di bulan tersebut.
Ikuti petunjuk pada kemasan tentang aturan penyimpanan.
Simpan pada suhu di bawah 30ºC.
Jangan mengkonsumsi Coplavix 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 Coplavix
Zat aktif di dalamnya adalah clopidogrel dan Asam asetilsalisilat. Tiap tablet mengandung 75 mg Clopidogrel (sebagai hydrogen sulfat) dan 100 mg Asam Asetilsalisilat.

Bahan lainnya adalah:
- Inti Tablet ASA: Maize starch, Asam stearate. Silica colloidal anhidrat, Microcristalline cellulose
- Penyalut ASA: Hipromellose 6 mPa.s, macrogol 6000 (8000), methacrilic acid-ethyl acrylate copolymer, talc, triethyl citrate
- Lapisan Clopidogrel: Lactose anhydrat, Hydroxypropylcellulose low substituted, macrogol 6000 (8000), All-Rac- *α*-tocopherol, partly pregelatinised starch, microcrystalline cellose, hydrogenated castor oil, sucrose stearate
- Penyalut Obat : Hypromellose mPa.s, Talc, Titanium dioxide, macrogol 6000 (8000), Simeticon
- Agen Poles: carnauba wax, talc.

Ciri-ciri Coplavix dan isi dalam kemasan
Coplavix 75/100 mg tablet salut enterik berbentuk oval, berwarna merah muda terang, di satu sisi terukir “C75” dan “A100” pada sisi lain. Coplavix tersedia dalam kemasan karton berisi 30 tablet, dalam blister yang berbahan PVC/PVDC/Aluminium atau yang seluruhnya berbahan aluminium.

DISETUJUI OLEH BPOM : 10/05/2022 ID : EREG10002212200061

HARUS DENGAN RESEP DOKTER
Coplavix 75/100 mg Reg No. DKI1977404315A1

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