COPLAVIX FILM-COATED TABLET 75MG/100 MG

QUALITATIVE AND QUANTITATIVE COMPOSITION

Clopidogrel hydrogen sulphate 97.875 mg (molar equivalent of 75 mg of clopidogrel base) and 111.11 mg of acetylsalicylic acid granulated with maize-starch corresponding to 100 mg of acetylsalicylic acid (ASA).
Excipients: lactose 8 mg, hydrogenated castor oil 3.3 mg.
For a full list of excipients, see section "*List of excipients*".

PHARMACEUTICAL FORM

Film-coated tablet.
CoPlavix tablets are light pink, oval, slightly biconvex, film-coated, 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 patients suffering from acute coronary syndrome:

- **Non-ST segment** elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction).

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

For further information please refer to section "*Pharmacodynamic properties*".

Posology and method of administration

Adults and elderly
CoPlavix fixed dose combination (FDC) should be given as a single daily 75 mg/100 mg dose. CoPlavix FDC is used in adult patients already taking both clopidogrel and ASA given separately at the appropriate dose, and replaces the individual clopidogrel and ASA product. It may be given with or without food.

- In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), treatment should be initiated with a single 300 mg loading dose of clopidogrel and an appropriate dose of ASA and then continued with CoPlavix 75 mg/100 mg once a day. 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*").

- 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*"). For patients greater than 75 years of age therapy should be initiated without a loading dose of clopidogrel. However, there is limited clinical experience in patients > 75 years of age.

Pharmacogenetics

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

Children and adolescents

- There is no experience in children. CoPlavix is not indicated for use in children or adolescents.

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.

Liver impairment

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

Contraindications
Due to the presence of both components of the product, CoPlavix is contraindicated in case of:

- Hypersensitivity to either of the active substances or the excipients of the medicinal product.

- severe liver 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 patients with known allergy to non-steroidal anti-inflammatory drugs (NSAIDs) products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of ASA may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).

- In patients with severe renal impairment (CrCL < 30 ml/min).

- In patients with active or history of peptic ulceration, haemophilia and other bleeding disorders

- Third trimester of pregnancy (see section "*Pregnancy and lactation*").

Special warnings and precautions for use

Bleeding and haematological disorders

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever 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) or thrombolytics. 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 be told that it might take longer than usual to stop bleeding when they take antiplatelet agents such as clopidogrel, ASA or both combined, 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 hemolytic anemia 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 insolated 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 P_{450} 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 drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. 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*").

Cross-reactivity among thienopyridines
Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since allergic 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 reactions such as thrombocytopenia and neutropenia. Patients who have had previous hypersensitivity to other thienopyridines should be carefully monitored for signs of hypersensitivity to clopidogrel during treatment.

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.

- Alcohol – Due to the presence of aspirin:
  - alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking ASA (see section "*Interaction with other medicinal products and other forms of interaction*").
  - patients should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking clopidogrel plus ASA

- This drug must be administered under close medical supervision in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of hemolysis (see section "*Undesirable effects*").

- Concomitant treatment with levothyroxine and salicylates, specifically at doses greater than 2.0 g/day, should be avoided (see section "*Interaction with other medicinal products and other forms of interaction*").

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 *(see* section *"Interactions").*

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

This medicinal product also contains hydrogenated castor oil which may cause stomach upset and diarrhea (see section *"List of excipients"*).

Interaction with other medicinal products and other forms of interaction
Drugs associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of drug associated with bleeding risk should be undertaken with caution.

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 (see Section "*Special warnings and precautions for use*")

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, co-administration 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 may be at risk of increased bleeding from trauma, surgery or other pathological conditions that 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. 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 CoPlavix should be co-administered with caution (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*").

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

Other concomitant therapy with clopidogrel: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. 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*").

Drugs that inhibit CYP2C19 include 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 administration 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 discourage (see section "Special w*arnings 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 in 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 medications to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital, 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 metabolized by CYP2C9 can be safely co-administered with clopidogrel.

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

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 should be used with caution with CoPlavix as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.
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.
Acetazolamide: Caution is recommended when co-administering salicylates with acetazolamide as there is an increased risk of metabolic acidosis.
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 (see section "*Special warnings and precautions for use*").
Levothyroxine: Salicylates, specifically at doses greater than 2.0 g/day, may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored (see section "*Special warnings and precautions for use*").

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.
Tenofovir: Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.
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.
Alcohol: Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking ASA (see section "*Special warnings and precautions for use*").
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 received a variety of concomitant medications including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.
Apart from the specific drug interaction information described above, interaction studies with CoPlavix and some drugs 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

Pregnancy and lactation

- Pregnancy

No clinical data on exposed pregnancies with CoPlavix are available, and no adequate data are available for clopidogrel alone. Animal studies have demonstrated a teratogenic effect arising from ASA. It is preferable not to use CoPlavix 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. (see section "*Preclinical safety data*").

- Lactation

Since ASA is known to be excreted in human breast milk and studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk, nursing is not recommended if treatment with CoPlavix is required.

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

Undesirable effects
Clinical studies experience:
Clopidogrel has been evaluated for safety in more than 42,000 patients, 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 effects 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. Clopidogrel 75 mg/day was well tolerated compared to ASA 325 mg/day in CAPRIE. The overall tolerability of clopidogrel in this study was similar to ASA, regardless of age, gender and race.

Haemorrhagic disorders:

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for ASA. In patients that received clopidogrel, gastrointestinal bleeding occurred at a rate of 2.0%, and required hospitalisation in 0.7%. In patients who received ASA, the corresponding rates were 2.7% and 1.1%, respectively.

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

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

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

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

The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months [clopidogrel plus ASA: 599/6259 (9.6%); ASA alone: 413/6303 (6.6%)], 1-3 months [clopidogrel plus ASA: 276/6123 (4.5%); ASA alone: 144/6168 (2.3%)], 3-6 months [clopidogrel plus ASA: 228/6037 (3.8%); ASA alone: 99/6048 (1.6%)], 6-9 months [clopidogrel plus ASA: 162/5005 (3.2%); ASA alone: 74/4972 (1.5%)], 9-12 months [clopidogrel plus ASA: 73/3841 (1.9%); ASA alone: 40/3844 (1.0%)].

There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel plus ASA vs. 5.3% ASA alone). 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 (17.4%) vs. the group taking ASA alone (12.9%). The incidence of major bleeding was similar between groups (1.3% versus 1.1% for the clopidogrel plus ASA group and the group taking ASA alone, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the clopidogrel plus ASA group and the group taking ASA alone, respectively) and intracranial haemorrhage (0.5% versus 0.7% in the clopidogrel plus ASA group and the group taking ASA alone, respectively) was low and similar in both groups.

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

Haematological disorders:

In CAPRIE, severe neutropenia (<0.45 x 10^9/l) was observed in 4 patients (0.04%) who received clopidogrel and 2 patients (0.02%) who received ASA. Two of the 9599 patients who received clopidogrel and none of the 9586 patients who received ASA had neutrophil counts of zero. One case of aplastic anaemia occurred on clopidogrel treatment.

The incidence of severe thrombocytopenia (<80 x 10^9/l) was 0.2% on clopidogrel and 0.1% on ASA.

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

Other clinically relevant adverse drug reactions pooled from clinical studies or that were spontaneously reported are presented in the table below according to the World Health Organisation classification. Their frequency is defined using the following conventions: common (>1/100, <1/10); uncommon (>1/1,000, < 1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare, not known***
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section "*Special warnings and precautions for use*"), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (see section "*Special warnings and precautions for use*"), bicytopenia, bone marrow failure

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Cardiac disorders				Kounis syndrome (in the context of a hypersensitivity reaction due to ASA)
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 outcome, especially in the elderly), headache, paraesthesia, dizziness		Taste disturbances, ageusia

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
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- Schönlein 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 ASA*, 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

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
				intestinal perforation)*; upper gastrointestinal 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 ASA and in patients with or without warning symptoms or a previous history of serious GI events*. Colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepatobiliary disorders				Acute liver failure, liver injury, mainly hepatocellular*, hepatitis, elevation of hepatic enzymes*, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnsons Syndrome, erythema multiforme), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticarial, eczema, lichen planus,

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
				fixed eruption, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)*, glomerulonephritis, blood creatinine increased, renal failure
Reproductive systems and breast disorders				Gynaecomastia
General disorders and administration site conditions	Bleeding at the 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”.

Overdose

There is no information concerning overdosage with CoPlavix.

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: Overdosage is manifested by the following symptoms:

- Moderate overdose: ringing in the ears, sensation of reduced hearing, headaches, vertigo.

- Severe overdose: fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory failure, severe hypoglycemia.

Overdose with salicylates, particularly in young children, can result in severe hypoglycaemia and potentially fatal poisoning.

In case of ASA severe overdose, the following actions should be undertaken: control of acid-base balance, forced alkaline diuresis, possibility of haemodialysis or peritoneal dialysis if necessary.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet $P2Y_{12}$ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

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

Repeated doses of 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 A_2, 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.

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 (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 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 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 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 plus ASA group and 1187 (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**.** The benefits observed with clopidogrel on top of ASA were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering drugs, beta blockers, and ACE inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily).

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) plus ASA or ASA alone (n=1739), (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.

<u>De-escalation of P2Y12 Inhibitor Agents in ACS</u>
Clopidogrel in combination with ASA is not indicated in STEMI patients undergoing PCI.

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).

Pharmacokinetic properties

Clopidogrel:

Absorption

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

Distribution

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

Metabolism

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

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

Elimination

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

Pharmacogenetics

Several polymorphic CYP450 enzymes activate clopidogrel. CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype. The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles correspond to reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for 85% of reduced function alleles in whites and 99% in Asians. Other alleles associated with reduced metabolism include CYP2C19*4, *5, *6, *7, and *8, but these are less frequent in the general population. Published frequencies for the common CYP2C19 phenotypes and genotypes are listed in the table below. Tests are available to determine a patient's CYP2C19 genotype.

CYP2C19 Phenotype and Genotype Frequency

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

A crossover study in 40 healthy adults, 10 each in the four CYP2C19 metaboliser group (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 150mg/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 300/75 mg dose regimen, antiplatelet response 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 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 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolises 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 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.

Acetylsalicyclic acid (ASA):
Absorption: Following absorption, the ASA in CoPlavix is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-1.5 hours of dosing, such that plasma levels of ASA are essentially undetectable 1.5-4 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 µg/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.
Metabolism 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 325 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 drug 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 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Core:
Mannitol (E421)
Macrogol 6000
Microcrystalline cellulose (low water content, 90 mcm)
Low substituted hydroxypropylcellulose
Hydrogenated castor oil
Stearic acid
Anhydrous colloidal silica
Coating:
Lactose
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Red iron oxide (E172)
Polishing agent:
Carnauba wax

Incompatibilities
Not applicable
Shelf-life
24 months
Special precautions for storage
Store below 25°C.
Store in the original package.
Nature and contents of container
14, 28, 30, 50, 84 and, 90, and 100 film-coated tablets packed in aluminium blister packs in cardboard cartons.
Not all pack sizes may be marketed.
Special precautions for disposal
No special requirements

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