

CO-PLAVIX DATA SHEET

NAME OF DRUG

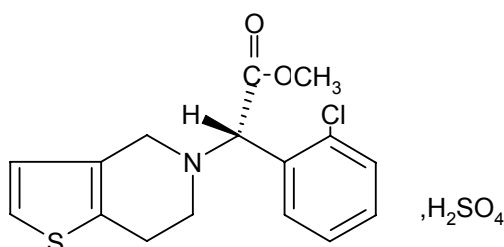
CO-PLAVIX* 75mg/100mg containing clopidogrel 75mg (as clopidogrel hydrogen sulfate) & aspirin 100mg

DESCRIPTION

Clopidogrel hydrogen sulfate is designated chemically as methyl (+)-(S)- α -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4H)-acetate sulfate (1:1).

The empirical formula of clopidogrel hydrogen sulfate is $C_{16}H_{16}ClNO_2S.H_2SO_4$ and its molecular weight is 419.9.

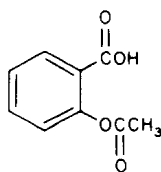
Clopidogrel hydrogen sulfate has the following chemical structure:



CAS Number: 120202-66-6 (Clopidogrel hydrogen sulfate),
113 665-84-2 (Clopidogrel base).

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

Aspirin (or acetylsalicylic acid) is designated chemically as 2-acetoxybenzoic acid and has the following chemical structure.



The empirical formula is $C_9H_8O_4$ and its molecular weight is 180.2.

The CAS number is 50-78-2.

Aspirin is a white crystalline powder or colourless crystals, odourless or almost odourless, slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether. It melts at about $135^\circ C$.

Co-Plavix tablets are film coated and for both strengths each tablet contains mannitol, macrogol 6000, microcrystalline cellulose, hydrogenated castor oil, hydroxypropylcellulose, maize starch, stearic acid, colloidal silica. The coating contains lactose, hypromellose, titanium dioxide, glycerol triacetate, a colourant and carnauba wax. The colourant is red iron oxide in Co-Plavix 75mg/100mg.

PHARMACOLOGY

Pharmacodynamics

Clopidogrel

Clopidogrel is a specific and potent inhibitor of platelet aggregation. Platelets have an established role in the pathophysiology of atherosclerotic disease and thrombotic events. Long term use of anti-platelet drugs has shown consistent benefit in the prevention of ischaemic stroke, myocardial infarction and vascular death in patients at increased risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. However, an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover (approximately 7 days).

Statistically significant and dose-dependent inhibition of platelet aggregation was noted 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 7 days after treatment was discontinued.

Aspirin

Aspirin 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.

Pharmacokinetics

Clopidogrel

After repeated oral doses of 75 mg per day, a single oral dose of clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/L) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative which represents about 85% of the circulating compound in plasma. Peak plasma levels of this metabolite (approx. 3 mg/L after repeated 75 mg oral doses) occurred approximately 1 hour after dosing.

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

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

Following an oral dose of ¹⁴C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120 hour interval after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

Plasma concentrations of the main circulating metabolite were significantly higher in elderly subjects (≥ 75 years) as compared to young healthy volunteers. However, these higher plasma levels were not associated with differences in platelet aggregation and bleeding time.

Plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 mL/min) and healthy subjects, after repeated doses of 75 mg/day. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day.

Aspirin

Absorption: Following absorption, the aspirin in Co-Plavix is hydrolysed to salicylic acid, with peak plasma levels of salicylic acid occurring within 1-1.5 hours of dosing, such that plasma levels of aspirin are essentially undetectable 1.5-4 hours after dosing.

Distribution: aspirin 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 aspirin in Co-Plavix is rapidly hydrolysed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for aspirin doses from 75 to 325 mg. This salicylic acid has a plasma half-life of approximately 2 hours. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide and a number of minor metabolites. 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 aspirin doses (10–20 g), the plasma half-life may be increased to over 20 hours. At high aspirin 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 pharmacokinetic interactions are unlikely.

Special Populations

Geriatric Patients:

Plasma concentrations of the main circulating metabolite of clopidogrel are significantly higher in the elderly (≥ 75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients:

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar in healthy volunteers receiving 75 mg of clopidogrel per day. Experience with clopidogrel plus aspirin is limited in patients with mild to moderate renal impairment. Therefore Co-Plavix should be used with caution in this population. Co-Plavix is contraindicated in severe renal impairment.

Patients with Hepatic Impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Co-Plavix should therefore be used with caution in this population. Co-Plavix is contraindicated in severe liver impairment.

Gender:

No significant difference was observed in the plasma levels of the main circulating metabolite of clopidogrel between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race:

Clopidogrel pharmacokinetic differences due to race have not been studied.

Clinical Trials

The safety and efficacy of clopidogrel and aspirin in patients with acute coronary syndrome has been evaluated in three double-blind studies: the CURE, CLARITY and COMMIT studies, which compared clopidogrel in combination with aspirin, to placebo with aspirin.

The **CURE** study included 12,562 patients with acute coronary syndrome (unstable angina or non-ST-elevation 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 = 6244) or placebo (n = 6287), both given in combination with aspirin (75-325 mg once daily) and other standard therapies (oral anti-coagulants and long term NSAIDs were not permitted). Patients were treated for up to one year.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p = 0.00009) for the clopidogrel-treated group. The benefits of clopidogrel were seen within a few hours and maintained throughout the course of the study (up to 12 months). The primary outcome was reduced to a similar extent within the first 30 days (relative risk reduction of 22%), from 30 days to one year (relative risk reduction of 19%), and for the entire one year study (relative risk reduction of 20%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischemia) was 1035 (16.5%) in the clopidogrel-treated group and 1187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p = 0.0005) for the clopidogrel-treated group, a benefit which was consistent for each component, indicating that clopidogrel reduced a range of atherothrombotic events.

In the course of the study, patients who underwent cardiac revascularisation (surgical or percutaneous coronary intervention with or without coronary stent implantation), received similar benefit from clopidogrel + aspirin (including standard therapies) as those who did not have a cardiac revascularisation.

The results obtained in populations with different characteristics (e.g. unstable angina or non-ST-elevation 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 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 aspirin (75-325 mg once daily).

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

The randomised, double-blind, placebo-controlled **CLARITY** trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation myocardial infarction and planned for thrombolytic therapy. Patients were randomised to receive either clopidogrel (300 mg loading

dose, followed by 75 to 162 mg/day; n = 1752) or placebo (n = 1739), together with aspirin (150 to 325 mg loading dose followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin for 48 hours. The patients were followed for 30 days.

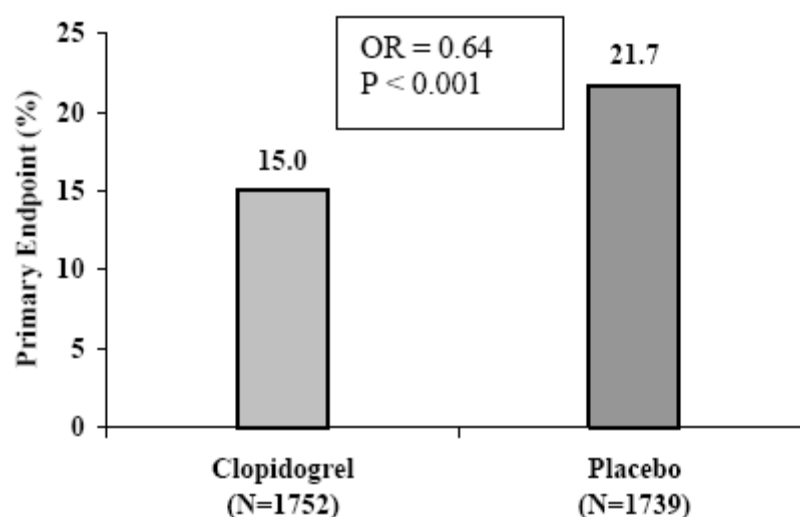
The primary endpoint was the occurrence of the composite of an occluded infarct-related artery (defined as TIMI Flow Grade 0 or 1) on the predischARGE angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by day 8 or by hospital discharge, if prior to day 8.

The patient population was mostly Caucasian (89.5%) and included 19.7% women and 29.2% were 65 years or over. 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.

The number of patients who reached the primary endpoint was 262 (15.0%) in the clopidogrel-treated group and 377 (21.7%) in the placebo group, representing an absolute reduction of 6.7% and a 36% reduction in the odds of the endpoint in favour of treatment with clopidogrel (95% CI: 0.53, 0.76; p<0.001), as shown in the figure below.

The benefit of clopidogrel on the primary endpoint was consistent across all prespecified subgroups, including patients' age, gender, infarct location and type of fibrinolytic or heparin used.

Event Rates for the Primary Composite Endpoint in the CLARITY Study



Based on odds of an occluded infarct-related artery (TFG 0/1), death or MI by angiography for clopidogrel versus placebo (OR: 0.64 [0.53 to 0.76]; p < 0.001)

The randomised, double-blind, placebo-controlled, 2x2 factorial design **COMMIT** trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected myocardial infarction with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients were randomised to receive clopidogrel (75 mg/day) or placebo, in combination with aspirin (162 mg/day), for 28 days or until hospital discharge, whichever came first.

The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The patient population included 27.8% women, 58.4% 60 years or over (26% 70 years or over) and 54.5% patients who received fibrinolytics, . 68% who received ACE-inhibitors and 10.9% who received non-trial beta-blockers (as well as half of the patients who received metoprolol as study medication).

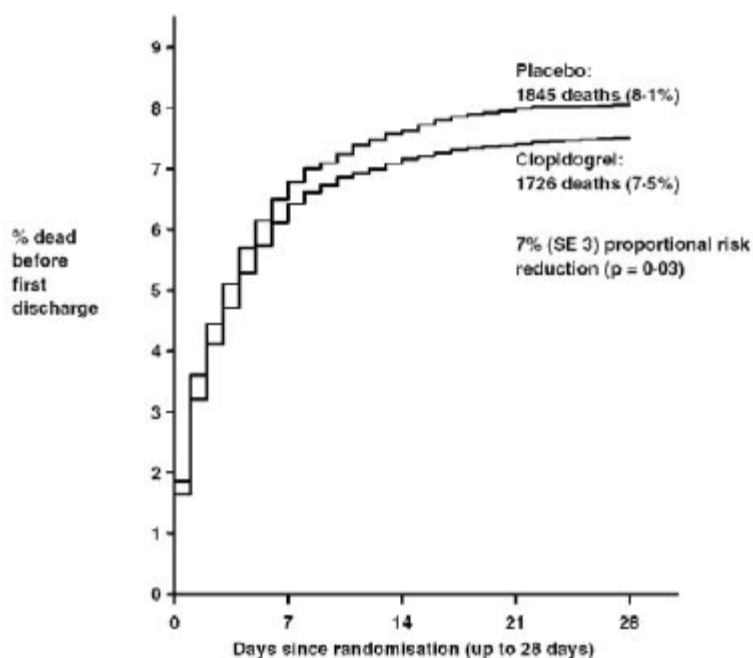
As shown in the table and figures below, clopidogrel significantly reduced the relative risk of death from any cause by 7% ($p = 0.029$) and the relative risk of the combination of re-infarction, stroke or death by 9% ($p = 0.002$), representing an absolute risk reduction of 5 and 9 patients per 1000 treated (0.5 and 0.9%), respectively.

Outcome Events in the COMMIT Analysis

Event	Clopidogrel +aspirin n = 22961	Placebo +aspirin n = 22891	Odds ratio (95% CI)	p-value
Composite endpoint:				
Death, MI or Stroke	2121 (9.2%)	2310 (10.1%)	0.91 (0.86, 0.97)	0.002
Death	1726 (7.5%)	1845 (8.1%)	0.93 (0.87, 0.99)	0.029
Non-fatal MI	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	0.011
Non-fatal Stroke	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.33

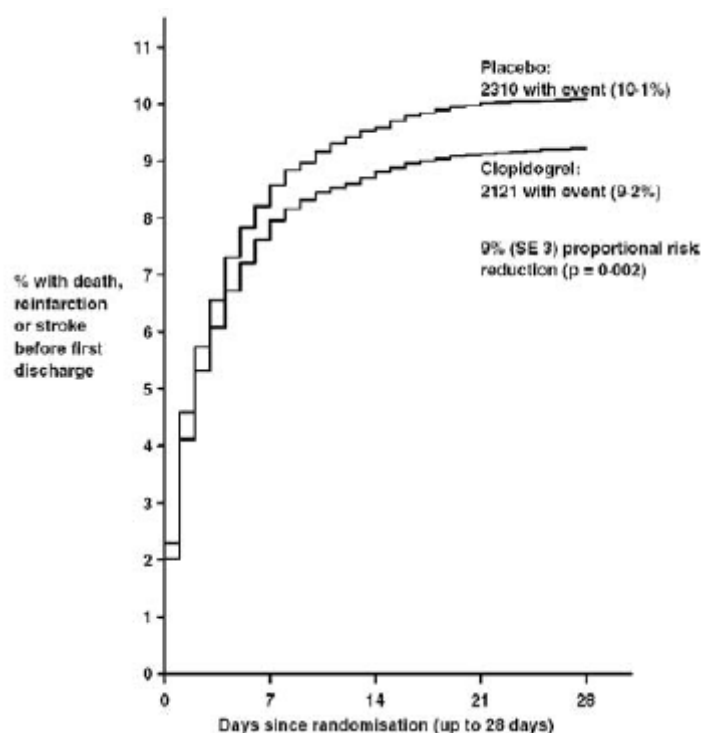
Note: 9 patients (2 clopidogrel and 7 placebo) suffered from both a non-fatal stroke and a non-fatal MI, hence the apparent disparity between composite endpoint and the sum of death, non-fatal MI and non-fatal stroke. Values for non-fatal MI and non-fatal stroke exclude patients who died of any cause.

Cumulative Event Rates for Death in the COMMIT Study*



* All treated patients received aspirin.

Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study *



* All treated patients received aspirin.

The benefit associated with clopidogrel on the combined endpoint was consistent across age, gender and with or without fibrinolytics and was observed as early as 24 hours.

The bioequivalence of CoPlavix to reference clopidogrel and aspirin tablets has been demonstrated in three open-label, randomized, single-dose, 2-sequence, 2-period, 2-treatment crossover studies. One study was performed with CoPlavix 75 mg/75 mg (BDR4659) and two with CoPlavix 75 mg/100 mg (BDR5000 and BEQ10600). Study BEQ10600 (CoPlavix 75 mg/100 mg) evaluated bioequivalence in 121 young healthy subjects based on clopidogrel and its inactive carboxylic acid metabolite, and aspirin and salicylic acid. Studies BDR4659 (CoPlavix[®] 75 mg/75 mg) and BDR5000 (CoPlavix 75 mg/100 mg) evaluated bioequivalence in 40 young healthy subjects based on clopidogrel inactive carboxylic acid metabolite, and aspirin and salicylic acid.

CoPlavix 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to the clopidogrel 75 mg tablets in terms of clopidogrel C_{max} and AUC, and/or carboxylic acid metabolite. For aspirin, CoPlavix[®] 75 mg/75 mg and 75/100 mg were demonstrated to be bioequivalent to aspirin 75 mg and 100 mg, respectively, in terms of aspirin AUC, and salicylic acid C_{max} and AUC. The 90% CIs for these parameters were entirely within the bioequivalence interval [0.80-1.25].

In terms of C_{max} , aspirin was not bioequivalent in the 3 studies, with the C_{max} being 1.3- to 1.6-fold higher for CoPlavix than for the aspirin tablets. However, considering the large number of aspirin formulations on the market and the clinical studies evaluating the benefit/risk of clopidogrel in combination with ASA (see above), a slight difference in ASA C_{max} is not considered to be clinically significant.

Mean (coefficient of variation %) exposure of clopidogrel and its inactive carboxylic acid metabolite after a single oral dose of Coplavix 75 mg/75 mg or 75 mg/100 mg and Plavix 75 mg

Compound	PK parameter	CoPlavix 75 mg/75 mg			CoPlavix 75 mg/100 mg					
		BDR4659			BDR5000			BEQ10600		
		CoPlavix	Plavix	90%CI	CoPlavix	Plavix	90%CI	CoPlavix	Plavix	90%CI
Clopidogrel	C _{max} (ng/mL)	Not assessed			Not assessed			2.49 (306)	2.23 (255)	0.94; 1.23
	AUC (ng.h/mL)	Not assessed			Not assessed			2.74 (210) ^a	2.72 (189) ^a	0.92; 1.15
Carboxylic acid metabolite	C _{max} (ng/mL)	3319 (26)	3105 (27)	0.99; 1.17	3042 (25)	2810 (26)	0.98; 1.20	3640 (30)	3590 (30)	0.96; 1.06
	AUC (ng.h/mL)	9215 (29)	8947 (27)	0.98; 1.07	8059 (19)	8004 (26) ^a	0.98; 1.07	9830 (25)	9860 (27)	0.98; 1.02

^an=39; ^bn=110; ^cn=111

Mean (coefficient of variation %) exposure of aspirin and salicylic acid after a single oral dose of Coplavix 75 mg/75 mg or 75 mg/100 mg and aspirin 75 mg or 100 mg

Compound	PK parameter	CoPlavix 75 mg/75 mg			CoPlavix 75 mg/100 mg					
		BDR4659			BDR5000			BEQ10600		
		CoPlavix	Aspirin	90%CI	CoPlavix	Aspirin	90%CI	CoPlavix	Aspirin	90%CI
Aspirin	C _{max} (ng/mL)	1207 (25)	738 (26)	1.51; 1.78	1492 (26)	964 (23)	1.41; 1.69	1580 (31)	1230 (35)	1.22; 1.39
	AUC (ng.h/mL)	936 (17)	826 (22) ^a	1.10; 1.20	1131 (16) ^a	1007 (21) ^b	1.08; 1.19	1440 (24) ^c	1300 (22) ^d	1.07; 1.13
Salicylic acid	C _{max} (ng/mL)	3533 (16)	3094 (17)	1.10; 1.20	4878 (14)	4189 (16)	1.12; 1.22	5390 (22)	5030 (21)	1.04; 1.10
	AUC (ng.h/mL)	12217 (21) ^a	11778 (19)	1.00; 1.06	17791 (32) ^a	17225 (30)	1.01; 1.05	21700 (29) ^c	20900 (28)	1.02; 1.04

^a: n=39; ^b: n=37; ^c: n=116; ^d: n=111

INDICATIONS

Co-Plavix is a fixed-dose combination product intended as continuation of therapy in patients with acute coronary syndrome already initiated with separate clopidogrel and aspirin products:

- Unstable angina or non-ST elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death and refractory ischaemia). CoPlavix is indicated for the treatment of acute coronary syndrome whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).
- ST-segment elevation acute myocardial infarction in order to prevent atherothrombotic events. In this population, Co-Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke in medically treated patients eligible for thrombolytic therapy.

CONTRAINDICATIONS

Due to the presence of both components of the product, Co-Plavix is contraindicated in case of:

- Hypersensitivity to clopidogrel, salicylates or any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as haemophilia, intracranial haemorrhage or gastrointestinal bleeding.
- Peptic ulcer or erosive gastritis
- Breast-feeding (see PRECAUTIONS-Pregnancy and Lactation).

In addition, due to the presence of aspirin, its use is also contraindicated in case of:

- Known allergy to Non-Steroidal Anti-inflammatory Drugs (NSAIDs) products and in patients with the syndrome of asthma with rhinitis and/or nasal polyps.
- Severe renal impairment.

PRECAUTIONS

General

As with the other anti-platelet agents, clopidogrel and aspirin prolong bleeding time and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions, as follows:

- If a patient is to undergo elective surgery and an anti-platelet effect is not desired, Co-Plavix should be discontinued at least 7 days prior to surgery.
- If the patient is at high risk of ophthalmic bleeding due to intraocular lesions clopidogrel should be used with extra caution.
- Co-Plavix should be used with caution in patients who have lesions with a propensity to bleed. Drugs that might induce such lesions (such as NSAIDs) are not recommended in patients taking Co-Plavix (See PRECAUTIONS-Interactions With Other Medicines).
- Co-Plavix should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper gastrointestinal symptoms, as this may be due to gastric ulceration which may lead to gastric bleeding.
- Gastrointestinal side effects, including stomach pain, heartburn, nausea, vomiting and gastrointestinal bleeding, may occur. Although minor upper gastrointestinal symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous gastrointestinal symptoms.
- Patients should be told about the signs and symptoms of gastrointestinal side effects and what steps to take if they occur. Patients should be told that it may take longer than usual for bleeding to stop when they take Co-Plavix, and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking Co-Plavix before any surgery is scheduled and before any new drug is taken.
- In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of aspirin and clopidogrel has been shown to increase major bleeding. Therefore, use of the combination of clopidogrel and aspirin should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.
- Due to the presence of aspirin, caution is required in patients with a history of asthma or allergic disorders (as they are at increased risk of hypersensitivity reactions) or with gout (as low doses of aspirin increase urate concentrations).
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

To prevent gastric irritation due to aspirin, CoPlavix should be taken with or after food .

Due to the presence of aspirin, caution is required in patients with a history of asthma or allergic disorders (as they are at increased risk of hypersensitivity reactions) or with gout (as low doses of aspirin increase urate concentrations).

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

The hypoglycaemic effect of chlorpropamide may be enhanced by the concurrent administration of aspirin. Large doses of aspirin may have intrinsic hypoglycaemic activity when given to diabetic patients, but the effects on carbohydrate metabolism are complex and it may cause hyperglycaemia

Tinnitus is a premonitory sign of salicylism but may not be detected in patients with hearing loss

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

CoPlavix is to be used under medical supervision only.

Coronary Artery Bypass Surgery

When coronary artery bypass surgery is to be performed, clopidogrel and aspirin should be suspended at least 5 days before surgery to reduce the risk of bleeding (see ADVERSE REACTIONS).

Pharmacogenetics

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

Renal Impairment

Experience with clopidogrel plus aspirin is limited in patients with mild to moderate renal impairment. Therefore Co-Plavix should be used with caution in this population. Patients should be observed closely for signs of salicylism. See also CONTRAINDICATIONS.

Hepatic Impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Co-Plavix should therefore be used with caution in this population. See also CONTRAINDICATIONS.

Ischaemic Stroke

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

Haematological

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 (plasma exchange).

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have also been reported very rarely in patients taking clopidogrel (see ADVERSE REACTIONS).

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. With chronic administration, occult blood loss may lead to iron deficiency anaemia. As with other anti-platelet agents, clopidogrel and aspirin 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 NSAIDs, heparin, glycoprotein IIb/IIIa inhibitors 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.

Carcinogenicity,

There was no evidence of carcinogenic effects when clopidogrel was given in the diet for 78 weeks to mice and 104 weeks to rats at doses up to 77 mg/kg per day (representing an exposure \approx 18 times the anticipated patient exposure, based on plasma AUC for the main

circulating metabolite in elderly subjects). Carcinogenicity studies have not been conducted with aspirin.

Genotoxicity

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by the oral route in mice).

Aspirin was not genotoxic in bacterial reverse mutation assays or in a recessive lethal mutation assay in *Drosophila*. However, there are conflicting results on the clastogenicity of aspirin in mammalian cells.

Effects on Fertility

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day)

Aspirin had antispermatogenic effects by inhibiting prostaglandin formation in Long-Evans rats at 250 mg/kg/day PO, but did not affect the fertility of male Wistar rats at 300 mg/kg/day IP. The clinical relevance of these observations is unknown.

Use in Pregnancy

Category C

Clopidogrel and/or its metabolites are known to cross the placenta in pregnant rats and rabbits. However, teratology studies in rats and rabbits at doses up to 500 mg and 300 mg/kg/day PO, respectively, revealed no evidence of embryotoxicity or teratogenicity.

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

Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the foetal ductus arteriosus, prolong labour and delay birth. Aspirin increases bleeding time both in the newborn infant and in the mother because of its anti-platelet effects.

No clinical data on exposed pregnancies with Co-Plavix are available and no adequate data are available for clopidogrel alone..

Co-Plavix should not be used in women during pregnancy unless the potential benefits outweigh the risks.

Use in Lactation

Breast-feeding is contraindicated during treatment with CoPlavix (See CONTRAINDICATIONS). Studies in rats have shown that clopidogrel and/or its metabolites are excreted in breast milk. Salicylates are excreted in breast milk. Chronic high doses of aspirin can cause adverse effects in the infant.

Interactions with alcohol

The effect of alcohol on the safety and efficacy of the combination of clopidogrel and aspirin has not been investigated in clinical trials. Concurrent ingestion of alcohol and aspirin may enhance occult blood loss and gastric irritation. In prolonged aspirin administration, occult blood loss may lead to iron deficiency anaemia. Aspirin inhibits ethanol dehydrogenase, a major enzyme in the first pass elimination of alcohol.

In vitro, the metabolism of clopidogrel has been shown to be altered in the presence of ethanol, such that clopidogrel is hydrolysed (inactivated) more slowly, and ethyl clopidogrel formed; the toxicity of ethyl clopidogrel has not been fully investigated.

Interactions with other medicines

Oral Anticoagulants (including warfarin)

The concomitant administration of Co-Plavix with warfarin is not recommended since it may increase the intensity of bleeding.

Injectable Anticoagulants

A pharmacodynamic interaction between Co-Plavix and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Glycoprotein IIb/IIIa inhibitors

Co-Plavix 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 IIa/IIb inhibitors.

Anti-platelet agents (such as eptifibatide, ticlopidine, tirofiban)

The effects of Co-Plavix and other drugs which inhibit platelet aggregation may be additive, leading to an increased risk of bleeding.

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 aspirin. The safety of concomitant administration of Co-Plavix with other thrombolytic agents has not been formally established and should be undertaken with caution.

Methotrexate

Due to the presence of aspirin, methotrexate and Co-Plavix should only be used together with caution, as aspirin can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Non Steroidal Anti-inflammatory Drugs (NSAIDs)

Aspirin may increase the risk of gastrointestinal side effects, including bleeding, when administered with NSAIDs. Aspirin displaces diclofenac from its binding sites, reducing diclofenac effectiveness.

The concomitant administration of ibuprofen with aspirin may limit the beneficial cardiovascular effects of aspirin in patients with increased cardiovascular risk.

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, there is a potential increased risk of gastrointestinal bleeding and NSAIDs and Co-Plavix should be co-administered with caution (See PRECAUTIONS).

Uricosuric agents (e.g. probenecid)

Caution is required because aspirin may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Drugs metabolised by Cytochrome P450 2C9

At high concentrations in vitro, the carboxylic acid metabolite of clopidogrel inhibits cytochrome P450 (2C9). Accordingly, Co-Plavix may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, warfarin, fluvastatin**, and many **non-steroidal anti-inflammatory agents**, but there are no data with which to predict the magnitude of these

interactions. Caution should be used when any of these drugs is co-administered with Co-Plavix.

Other concomitant therapy

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.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics:

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including aspirin or COX-2 inhibitors) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy and periodically thereafter.

Interactions with higher dose aspirin

Interactions with the following medicines with higher (anti-inflammatory) doses of aspirin have been reported: alendronate, angiotensin converting enzyme (ACE) inhibitors, anticonvulsants (phenytoin and valproic acid), beta blockers, systemic corticosteroids, diuretics, selective serotonin reuptake inhibitors (SSRIs), spironolactone, verapamil, hypoglycaemic agents and zafirlukast. However, more than 30 000 patients entered into clinical trials with clopidogrel plus aspirin at maintenance doses lower than or equal to 325mg, received a variety of concomitant medications, including diuretics, beta blockers, ACE inhibitors, calcium channel antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), anti-epileptic agents, hormone replacement therapy and GPIIb/IIIa antagonists, without evidence of clinically significant adverse interactions.

Effects on ability to drive and use machines

Co-Plavix has no or negligible influence on the ability to drive and use machines.

ADVERSE REACTIONS

Clopidogrel

Clopidogrel has been evaluated for safety in more than 42,000 patients, including over 30 000 patients treated with clopidogrel plus aspirin and over 9,000 patients treated for 1 year or more. The clinically relevant adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

The CAPRIE study included 19 185 patients with established atherosclerosis or history of atherothrombosis as manifested by myocardial infarction, ischaemic stroke or peripheral arterial disease. Patients were randomised to clopidogrel 75 mg/day or aspirin 325 mg/day, and were followed for 1 to 3 years. Clopidogrel was well tolerated compared to aspirin in the CAPRIE trial. The overall tolerability of clopidogrel in this study was similar to aspirin, regardless of age, gender and race. The clinically relevant adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

Haemorrhagic disorders

In CAPRIE, the overall incidence of any bleeding in patients treated with either clopidogrel or aspirin was similar (9.3%). The incidence of severe bleeds was 1.4% in the clopidogrel group and 1.6% in the aspirin group.

Gastrointestinal haemorrhage was significantly less frequent with clopidogrel (1.99%) compared to aspirin (2.66%). The incidence of intracranial haemorrhage was 0.35% for clopidogrel compared to 0.49% for aspirin.

In CURE, the administration of clopidogrel + aspirin as compared to placebo + aspirin, was not associated with an increase in life-threatening or fatal bleeds (event rates 2.2% vs. 1.8% and 0.2% vs. 0.2%, respectively). The incidence of intra-cranial bleeding was 0.1% in both groups.

There was a significant difference between the two treatment groups for other types of bleeding: non life- threatening major bleeds (1.6% clopidogrel + aspirin vs. 1.0% placebo + aspirin), primarily gastrointestinal and at puncture sites, and minor bleeds (5.1% clopidogrel + aspirin vs. 2.4% placebo + aspirin). The major bleeding event rate for clopidogrel + aspirin was dose-dependent on aspirin (100mg: 2.6%; 100-200mg: 3.5%; 200mg: 4.9%) as was the major bleeding event rate for placebo + aspirin (<100mg: 2.0%; 100-200mg: 2.3%; <200mg: 4.0%).

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 + aspirin vs. 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + aspirin, and 6.3% for placebo + aspirin.

In CLARITY the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in haemoglobin > 5 g/dL) was similar between groups (1.3% versus 1.1% in the clopidogrel + aspirin and the placebo + aspirin groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the clopidogrel + aspirin and in the placebo + aspirin groups, respectively) and intracranial haemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of non-cerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups, as shown in the table below.

Number of Patients with Bleeding Events in COMMIT

Type of bleeding	Clopidogrel + aspirin (n = 22961)	Placebo + aspirin (n = 22891)	p-value
Major * non-cerebral or cerebral bleeding	134 (0.6%)	125 (0.5%)	0.59
Major non-cerebral	82 (0.4%)	73 (0.3%)	0.48
Fatal	36 (0.2%)	37 (0.2%)	0.90
Haemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.91
Fatal	39 (0.2%)	41 (0.2%)	0.81
Other non-cerebral bleeding (non major)	831 (3.6%)	721 (3.1%)	0.005
Any non-cerebral bleeding	896 (3.9%)	777 (3.4%)	0.004

*Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion

Haematological disorders

In CAPRIE, patients were intensively monitored for thrombocytopenia and neutropenia.

Clopidogrel was not associated with an increase in the incidence of thrombocytopenia compared to aspirin. Very rare cases of platelet count $\leq 30 \times 10^9/L$ have been reported.

Severe neutropenia ($<0.45 \times 10^9/L$) was observed in four patients (0.04%) that received clopidogrel and in two patients that received aspirin. Two of the 9599 patients who received clopidogrel and none of the patients who received aspirin had a neutrophil count of zero. One of the clopidogrel treated patients was receiving cytostatic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with clopidogrel.

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

Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other signs of infection.

Gastrointestinal

In CAPRIE, overall the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel was significantly lower than in those receiving aspirin. The incidence of peptic, gastric, or duodenal ulcers was 0.68% for clopidogrel and 1.15% for aspirin. Cases of diarrhoea were reported at a higher frequency in the clopidogrel group (4.46%) compared to the aspirin group (3.36%).

In CURE, there was no significant difference in the incidence of non-haemorrhagic gastrointestinal effects in the clopidogrel or placebo groups.

In CLARITY, the incidence of gastrointestinal adverse events was 6.9% for clopidogrel treated patients, compared to 7.2% in placebo treated patients.

In COMMIT, 2 patients reported gastrointestinal adverse events in the clopidogrel treated group, compared to one in the placebo treated group.

Rash

In CAPRIE, there were significantly more patients with rash in the clopidogrel group (4.2%) compared to the aspirin group (3.5%).

In CURE, rash occurred in more patients in the clopidogrel group.

In CLARITY, 0.7% of patients in the clopidogrel group reported a rash, compared to 0.5% in the placebo group.

Treatment Discontinuation

In the clopidogrel and aspirin treatment groups of the CAPRIE study, discontinuation due to adverse events occurred in approximately 13% of patients after 2 years of treatment. Adverse

events occurring in $\geq 2.5\%$ of patients on clopidogrel in the CAPRIE controlled clinical trial are shown in the table below regardless of relationship to clopidogrel. The median duration of therapy was 20 months, with a maximum of 3 years.

In CURE, the overall incidence of discontinuation due to adverse events was greater in the clopidogrel group than in the placebo group (366 [5.8%] and 247 [3.9%] patients, respectively), with the main differences being in events in the platelet, bleeding and clotting disorders (1.1% versus 0.7%) and skin disorders (0.7% versus 0.3%). The increase in the rate of study drug discontinuation due to non-hemorrhagic adverse events was primarily due to the increase in rash seen in the clopidogrel group. There was no apparent difference between the 2 treatment groups in the rates of discontinuations due to other adverse events.

In CLARITY, the overall incidence of discontinuation due to adverse events was greater in the placebo group compared with the clopidogrel group (6.9% for clopidogrel treated patients compared to 8.6% for placebo treated patients).

In COMMIT, the overall incidence of discontinuation due to adverse events was similar in each treatment group (2.4% for clopidogrel treated patients compared to 2.2% for placebo treated patients).

Adverse events occurring in $\geq 2.5\%$ of patients receiving Clopidogrel in CAPRIE and CURE

BODY SYSTEM/EVENT	CAPRIE		CURE	
	% Incidence (% discontinuation)		% Incidence (% discontinuation)	
	Clopidogrel n = 9599	Aspirin n = 9586	Clopidogrel + aspirin n = 6259	Placebo + aspirin n = 6303
Body as a Whole - general disorders				
Chest pain	8.3 (0.2)	8.3 (0.3)	2.7 (0.02)	2.8 (0.0)
Accidental/inflicted injury	7.9 (0.1)	7.3 (0.1)	1.1 (0.06)	1.2 (0.03)
Influenza like symptoms	7.5 (<0.1)	7.0 (<0.1)	1.1 (0.0)	1.1 (0.0)
Pain	6.4 (0.1)	6.3 (0.1)	1.3 (0.02)	1.4 (0.0)
Fatigue	3.3 (0.1)	3.4 (0.1)	1.5* (0.02)	1.0 (0.0)
Cardiovascular disorders - general				
Hypertension	4.3 (<0.1)	5.1* (<0.1)	0.9 (0.0)	0.9 (0.0)
Central and peripheral nervous system disorders				
Headache	7.6 (0.3)	7.2 (0.2)	3.1 (0.08)	3.2 (0.10)
Dizziness	6.2 (0.2)	6.7 (0.3)	2.4 (0.08)	2.0 (0.02)
Gastrointestinal				
Abdominal pain	5.6 (0.7)	7.1* (1.0)	2.3 (0.26)	2.8 (0.27)
Dyspepsia	5.2 (0.6)	6.1* (0.7)	2.0 (0.08)	1.9 (0.02)
Diarrhoea	4.5* (0.4)	3.4 (0.3)	2.1 (0.11)	2.2 (0.13)
Nausea	3.4 (0.5)	3.8 (0.4)	1.9 (0.18)	2.3 (0.08)
Metabolic and nutritional disorders				
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)	0.1 (0.0)	0.2 (0.0)
Musculoskeletal system disorders				
Arthralgia	6.3 (0.1)	6.2 (0.1)	0.9 (0.0)	0.9 (0.0)
Back pain	5.8 (0.1)	5.3 (<0.1)	1.0 (0.03)	1.2 (0.0)
Myo-, endo-, pericardial and valve disorders				
Angina pectoris	10.1 (0.6)	10.7 (0.4)	0.1 (0.0)	0.1 (0.0)
Coronary artery disorder	6.2 (0.3)	5.6 (0.3)	0.03 (0.0)	0.06 (0.0)

Platelet, bleeding and clotting disorders				
Purpura	5.3* (0.3)	3.7 (0.1)	0.3 (0.0)	0.1 (0.0)
Epistaxis	2.9 (0.2)	2.5 (0.1)	0.2 (0.08)	0.1 (0.02)
Psychiatric disorders				
Depression	3.6 (0.1)	3.9 (0.2)	0.7 (0.02)	0.7 (0.0)
Resistance mechanism disorders				
Infection	4.7 (<0.1)	4.2 (0.1)	1.3 (0.0)	1.2 (0.0)
Respiratory system disorders				
Upper respiratory tract infection	8.7 (<0.1)	8.3 (<0.1)	1.1 (0.0)	1.0 (0.0)
Dyspnoea	4.5 (0.1)	4.2 (0.1)	1.9 (0.0)	1.9 (0.02)
Rhinitis	4.2 (0.1)	4.2 (<0.1)	0.2 (0.0)	0.1 (0.0)
Bronchitis	3.7 (0.1)	3.7 (0)	1.1 (0.0)	1.5 (0.0)
Coughing	3.1 (<0.1)	2.7 (<0.1)	1.3 (0.0)	1.2 (0.0)
Skin and appendage disorders				
Rash	4.2* (0.5)	3.5 (0.2)	1.3 (0.29)	1.1 (0.14)
Pruritus	3.3* (0.3)	1.6 (0.1)	0.5 (0.11)	0.5 (0.05)
Urinary system disorders				
Urinary tract infection	3.1 (0)	3.5 (0.1)	1.5 (0.0)	1.4 (0.0)
Vascular (extracardiac) disorders				
Claudication intermittent	3.8 (0.2)	3.8 (0.2)	0.1 (0.02)	0.1 (0.0)
Peripheral ischaemia	3.2 (0.2)	3.4 (0.2)	0.4 (0.03)	0.3 (0.0)
Cerebrovascular disorder	2.6 (0.3)	2.9 (0.3)	0.3 (0.03)	0.4 (0.03)

* indicates statistical significance ($p \leq 0.05$)

Incidence of discontinuation, regardless of relationship to therapy is shown in parentheses.

Clinically relevant adverse reactions not listed above pooled from CAPRIE, CURE, CLARITY and COMMIT studies with an incidence of $\geq 0.1\%$ as well as all serious and relevant adverse reactions are listed below according to the World Health Organisation classification. Their frequency is defined using the following conventions: *common*: $> 1/100$ (1%) and $< 1/10$ (10%); *uncommon*: $\geq 1/1000$ (0.1%) and $< 1/100$ (1%) and *rare*: $\geq 1/10000$ (0.01%) and $< 1/1000$ (0.1%).

Central and peripheral nervous system disorders

Uncommon: Paraesthesia

Rare: Vertigo

Gastrointestinal system disorders

Uncommon: Flatulence, constipation, vomiting, gastric, peptic or duodenal ulcer

Platelet, bleeding and clotting disorders

Uncommon: Bleeding time increased

White cell and RES disorders

Uncommon: Leucopenia and eosinophilia

Post-Marketing Experience

The following have been reported spontaneously from worldwide post-marketing experience with clopidogrel:

Note *very common* $\geq 1/10$ ($\geq 10\%$)

common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)

uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1.0\%$)

rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)
very rare $< 1/10,000$ ($< 0.01\%$)

Musculoskeletal, connective and bone

Very rare: Arthralgia, arthritis, myalgia

Immune system disorders

Very rare: anaphylactoid reactions, serum sickness

Vascular disorders

Very rare: vasculitis, hypotension

Blood and lymphatic system disorders

Very rare: serious cases of bleeding, mainly skin, musculo-skeletal (haemarthrosis, haematoma), eye (conjunctival, ocular, retinal) and respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), epistaxis, haematuria and haemorrhage of operative wound. Fatal haemorrhage, including intracranial, gastrointestinal and retroperitoneal haemorrhage. Cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with aspirin or clopidogrel with aspirin and heparin (see Interactions with Other Medicines)

Very rare cases of thrombotic thrombocytopenic purpura (TTP) have been reported.

Very rare: Agranulocytosis, aplastic anaemia, neutropenia, pancytopenia, granulocytopenia, anaemia

Uncommon: eosinophilia, leucopenia, decreased neutrophils, decreased platelets, increased bleeding time

Skin and subcutaneous tissue disorders

Very rare: macropapular or erythematous rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) eczema, lichen planus

Psychiatric

Very rare: confusion, hallucinations

Nervous system disorders

Very rare: taste disturbances

Hepatobiliary disorders

Very rare: hepatitis, acute liver failure

Gastrointestinal disorders

Very rare: colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

Respiratory, thoracic and mediastinal disorders

Very rare: bronchospasm, interstitial pneumonitis

Renal and Urinary disorders

Very rare: glomerulopathy

Investigations

Very rare: blood creatinine increase, abnormal liver function tests

General disorders and administration site conditions

Very rare: fever, syncope

Aspirin

In addition to some of the adverse reactions listed above, aspirin is associated with the following adverse effects.

Aspirin produces a prolongation of the bleeding time and may produce epigastric distress, nausea and vomiting, gastric or duodenal ulcers and erosive gastritis which may lead to serious gastrointestinal bleeding. These side effects are more likely to occur when higher doses are administered, although they may also occur when low doses are used.

Iron deficiency anaemia may develop as a result of occult gastrointestinal bleeding when aspirin is used for long periods of time.

Aspirin may cause haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

Aspirin may cause tinnitus or hearing loss.

DOSAGE AND ADMINISTRATION

Adults

In patients with:

- unstable angina or non-ST elevation myocardial infarction acute coronary syndrome – treatment should be initiated with a single 300 mg loading dose of clopidogrel plus aspirin (75mg-325mg). Subsequently, long-term treatment should be continued with one Co-Plavix tablet once a day taken with or without food.
- ST elevation acute myocardial infarction –treatment should be initiated as soon as possible after symptoms start with clopidogrel (75mg or a single loading dose of 300mg) plus aspirin with or without thrombolytics. Subsequently, daily treatment should continue with one Co-Plavix tablet once a day taken with or without food.

No dosage adjustment is necessary for elderly patients (See Pharmacology: Special Populations).

Do not halve tablet. Dose equivalence when the tablet is divided has not been established

Children and Adolescents

Safety and efficacy in subjects below the age of 18 have not been established.

There is a possible association between aspirin and Reye's syndrome when aspirin is given to children. Reye's syndrome is a very rare disease which can be fatal.

POISONING AND OVERDOSAGE

There is no information concerning overdosage with Co-Plavix.

In animals, clopidogrel at single oral doses ≥ 1500 mg/kg caused necrotic-haemorrhagic gastritis, oesophagitis and enteritis in mice, rats and baboons. Necrotic tubulopathy and tubulo-interstitial nephritis were also noted in mice.

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleeding is 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.

Aspirin overdosage is manifested by the following symptoms:

- Moderate overdosage: tinnitus, hearing loss, headaches, vertigo
- Severe overdosage: fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory failure, severe hypoglycaemia.

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

MEDICINE CLASSIFICATION

Prescription Medicine

PRESENTATION

CoPlavix tablets are light pink, oval, slightly biconvex, film-coated, engraved with "C75" on one side and "A100" on the other side.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established

Store below 25°C.

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