

CLOPIDEV

Clopidogrel besilate

Presentation

CLOPIDEV 75mg film-coated tablets. White to off-white, marbled, round, biconvex film-coated tablets. Each film-coated tablet contains 75mg of clopidogrel (as besilate). For a full list of excipients, see **Further Information**.

Uses

Actions

Pharmacotherapeutic group: platelet aggregation inhibitors excluding heparin, ATC Code: B01AC-04.

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. 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).

Repeated doses of 75mg 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 75mg 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.

Clinical Trials

The safety and efficacy of clopidogrel have been evaluated in 4 double-blind studies involving over 80,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75mg/day or ASA 325mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p = 0.045), which corresponds, for every 1,000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at $p = 0.003$) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR = 7.3%; CI: -5.7 to 18.7 [$p = 0.258$]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR = -4.0%; CI: -22.5 to 11.7 [$p = 0.639$]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤ 75 years.

Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

Acute coronary syndrome

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemic or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300mg loading dose followed by 75mg/day, N = 6,259) or placebo (N = 6,303), both given in combination with ASA (75-325mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel and placebo was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; $p = 0.00009$) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG). New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted (see **Warnings and Precautions**).

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 1,035 (16.5%) in the clopidogrel-treated group and 1,187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, $p = 0.0005$) for the clopidogrel-treated group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel treated group and 363 (5.8%) in the placebo treated group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia).

Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering medicinal products, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325mg 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 (300mg loading dose, followed by 75mg/day, n = 1752) or placebo (n = 1,739), both in combination with ASA (150 to 325mg as a loading dose, followed by 75 to 162mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischARGE angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients \geq 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint, representing an absolute reduction of 6.7% and a 36% odds reduction in favour 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 pre-specified 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 (75mg/day, n = 22,961) or placebo (n = 22,891), in combination with ASA (162mg/day), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients \geq 60 years (26% \geq 70 years) and 54.5% patients who received fibrinolytics.

Clopidogrel significantly reduced the relative risk of death from any cause by 7% ($p = 0.029$), and the relative risk of the combination of re-infarction, stroke or death by 9% ($p = 0.002$), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

Pharmacokinetics

After repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025mg/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. 3mg/L after repeated 75mg oral doses) occurred approximately 1 hour after dosing.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by Cytochrome P450 isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly

to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

The kinetics of the main circulating metabolite were linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150mg 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 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. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

The pharmacokinetics and pharmacodynamics of clopidogrel were assessed in a single and multiple dose study in both healthy subjects and those with cirrhosis (Child-Pugh class A or B). Daily dosing for 10 days with clopidogrel 75mg/day was safe and well tolerated. Clopidogrel C_{max} for both single dose and steady state for cirrhotics was many fold higher than in normal subjects. However, plasma levels of the main circulating metabolite together with the effect of clopidogrel on ADP-induced platelet aggregation and bleeding time were comparable between these groups.

Special Populations

Geriatric patients

Plasma concentrations of the main circulating metabolite 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 75mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60mL/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 75mg of clopidogrel per day. No dosage adjustment is needed in renally impaired patients. However, experience with clopidogrel is limited in patients with severe renal impairment. Therefore clopidogrel should be used with caution in this population.

Gender

No significant difference was observed in the plasma levels of the main circulating metabolite 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 Ischaemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race

Pharmacokinetic differences due to race have not been studied.

Indications

Prevention of vascular ischaemia associated with atherothrombotic events (MI, stroke and vascular death) in patients with a history of symptomatic atherosclerotic disease.

Acute Coronary Syndrome

CLOPIDEV is indicated in combination with aspirin for patients with:

- Unstable angina or non-ST elevation MI. CLOPIDEV is indicated for early and long-term reduction of atherothrombotic events (myocardial infarction, stroke, vascular death and refractory ischaemia) whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).
- ST-segment elevation acute myocardial infarction. In this population, clopidogrel 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.

Dosage and Administration

Clopidogrel should be taken once a day with or without food.

Adults

Generally, clopidogrel should be given as a single daily dose of 75mg.

In patients with acute coronary syndrome:

- Unstable angina or non-ST elevation myocardial infarction – clopidogrel treatment should be initiated with a single 300mg loading dose and then continued long-term at 75mg once a day (with aspirin 75mg-325mg daily).
- ST elevation acute myocardial infarction – clopidogrel treatment should be given as a single daily dose of 75mg initiated with or without a 300mg loading dose in combination with aspirin and with or without thrombolytics.

No dosage adjustment is necessary for either elderly patients or patients with renal impairment (see **Pharmacokinetics**).

Children and Adolescents

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

Contraindications

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

Warnings and Precautions

As with the other anti-platelet agents, clopidogrel prolongs 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, clopidogrel should be discontinued at least 5 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.
- Although clopidogrel has shown a lower incidence of gastrointestinal bleeding compared to aspirin in a large controlled clinical trial (CAPRIE), the drug should be used with caution in patients who have lesions with a propensity to bleed. Drugs that might induce such lesions (such as aspirin and Non-Steroidal Anti-Inflammatory Drugs) should be used with caution in patients taking clopidogrel. (See **Precautions – Interactions with other drugs**).
- Patients should be told that it may take longer than usual for bleeding to stop when they take clopidogrel (alone or in combination with aspirin), and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.
- 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, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

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

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

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

Coronary Artery Bypass Surgery

When coronary artery bypass surgery is to be performed, clopidogrel should be suspended at least 5 days before surgery to reduce the risk of bleeding (see **Adverse Effects**).

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.

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 Effects**).

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. As with other anti-platelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with aspirin, non-steroidal anti-inflammatory drugs, 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.

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

Use in Pregnancy

Category B1.

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 500mg and 300mg/kg/day PO, respectively, revealed no evidence of embryotoxicity or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should not be used in women during pregnancy.

Use in Lactation

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in breast milk (see **Contraindications**).

Effects on Ability to Drive and Use Machines

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

Adverse Effects

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies are discussed below. Overall the tolerability of clopidogrel 75mg/day was comparable to ASA 325mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

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

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

In CURE, the major bleeding event rate for clopidogrel + ASA was dose-dependent on ASA (<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo + ASA (<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 month (clopidogrel: 9.6%; placebo: 6.6%), 1-3 months (clopidogrel: 4.5%; placebo: 2.3%), 3-6 months (clopidogrel: 3.8%; placebo: 1.6%), 6-9 months (clopidogrel: 3.2%; placebo: 1.5%), 9-12 months (clopidogrel: 1.9%; placebo: 1.0%). There was no excess in major bleeds with clopidogrel + ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel + ASA vs 5.3% placebo + ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + ASA, and 6.3% for placebo + ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel + ASA group (17.4%) vs the placebo + ASA group (12.9%). The incidence of major bleeding was similar between groups (1.3% vs 1.1% for the clopidogrel + ASA and the placebo + ASA groups, respectively). This was

consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

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

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%) who received clopidogrel and in two patients who received aspirin. Two of the 9,599 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.

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% vs 0.7%) and skin disorders (0.7% vs 0.3%). The increase in the rate of study drug discontinuation due to non-haemorrhagic 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 reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP) (see Warnings & Precautions) aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	

Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

Interactions

Oral anticoagulants: The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see **Warnings and Precautions**).

Glycoprotein IIb/IIIa inhibitors: Clopidogrel 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 **Warnings and Precautions**).

Acetylsalicylic acid (ASA): A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see **Warnings and Precautions**). However, clopidogrel and ASA have been administered together for up to one year (see **Actions**).

Heparin: A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see **Warnings and Precautions**).

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 **Adverse Effects**). However, the use of clopidogrel with other thrombolytic agents should be undertaken with caution.

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

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

Drugs Metabolised by Cytochrome P450 2C9

At high concentrations *in vitro*, clopidogrel inhibits cytochrome P450 (2C9). Accordingly, CLOPIDEV 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 CLOPIDEV.

Other Concomitant Therapy

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 and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g. omeprazole) should be discouraged.

In addition to the above specific interaction studies, patients entered into clinical trials with clopidogrel received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), anti-epileptic agents, GPIIb/IIIa antagonists and hormone replacement therapy without evidence of clinically significant adverse interactions.

Overdosage

Overdosage 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.

Pharmaceutical Precautions

List of Excipients

Tablet core:

Macrogol 6000
Cellulose, microcrystalline (E460)
Crospovidone type A
Castor oil, hydrogenated

Film-coating:

Macrogol 6000
Ethylcellulose (E462)
Titanium dioxide (E171)

Incompatibilities

Not applicable.

Shelf Life

3 years.

Special Precautions for Storage

Store below 25°C in the original blister in order to protect from moisture.

Special Precautions for Disposal

No special requirements.

Medicine Classification

Prescription Medicine.

Package Quantities

Alu-Alu blisters containing 28 film-coated tablets packed in cardboard cartons.

Further Information

Preclinical Safety Data

During non clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75mg/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 77mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

Name and Address

Distributed in New Zealand by:
Deva Holdings (NZ) Ltd
C/- Pharmaco (NZ) Ltd
P O Box 4079
Auckland 1140

Date of Preparation

6 December 2009