

Arrow - Clopidogrel

Clopidogrel Tablets 75mg

Presentation

Arrow - Clopidogrel is a white, round tablet, with 'CP' on one side and 'S' on other side. Each tablet contains 75 mg of clopidogrel.

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

Uses

Actions

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 antiplatelet 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.

Pharmacokinetics

Absorption

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.

Distribution and metabolism

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 (approximately 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.

Plasma concentrations of the main circulating metabolite were significantly higher in elderly subjects (greater than or equal to 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 5 - 15 mL/minute) compared to subjects with moderate renal disease (creatinine clearance 30 - 60 mL/minute) 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.

Elimination

Following an oral dose of ¹⁴C-labelled clopidogrel in humans, 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.

Special patient groups

Geriatric patients

Plasma concentrations of the main circulating metabolite are significantly higher in the elderly (greater than or equal to 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.

Renal impairment

After repeated doses of clopidogrel 75 mg per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance 5 to 15 mL/minute) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/minute) 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 clopidogrel 75 mg 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 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.

Clinical trials

The safety and efficacy of clopidogrel in preventing vascular ischaemic events have been evaluated in four double blind studies, the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study, a comparison of clopidogrel to aspirin and the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events), CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) and COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) studies, which compared clopidogrel in combination with aspirin, to placebo with aspirin.

Myocardial infarction or stroke, or established peripheral arterial disease

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.

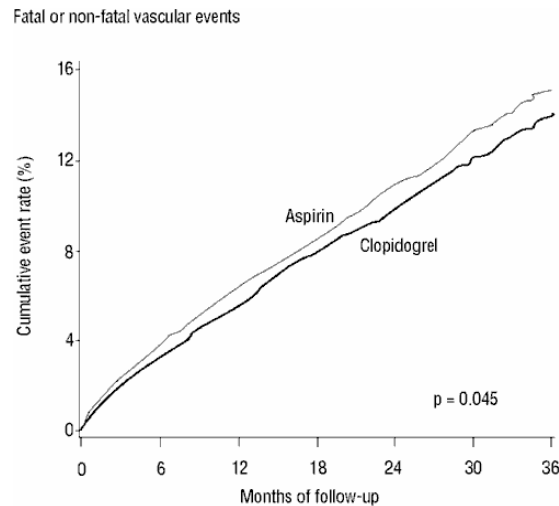
The trial's primary outcome was the time to first occurrence of new ischaemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

Patients	Clopidogrel 9,599	Aspirin 9,586
Ischaemic stroke (fatal or not)	438 (4.56%)	461 (4.81%)
Myocardial infarction (fatal or not)	275 (2.86%)	333 (3.47%)
Other vascular death	226 (2.35%)	226 (2.36%)
Total	939 (9.78%)	1,020 (10.64%)

As shown in the table above, clopidogrel was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.78 versus 10.64%) was 8.7%, $p = 0.045$. Similar results were obtained when all cause mortality and all

cause strokes were counted instead of vascular mortality and ischaemic strokes (risk reduction 6.9%). In patients who survived an on-study stroke or myocardial infarction, the incidence of subsequent events was again lower in the clopidogrel group.

The curves indicating the overall event rate are shown in the figure below. The event curves separated early and continued to diverge over a 3-year follow-up period.



Acute coronary syndrome

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 = 6,244) or placebo (n = 6,287), both given in combination with aspirin (75 - 325 mg once daily) and other standard therapies [oral anticoagulants and long-term non-steroidal anti-inflammatory drugs (NSAIDs) were not permitted]. Patients were treated for up to 1 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 1 year (relative risk reduction of 19%), and for the entire 1-year study (relative risk reduction of 20%).

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, 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 plus 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) 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 or 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 an ST elevation myocardial infarction and planned for thrombolytic therapy. Patients were randomised to receive either clopidogrel (300 mg loading dose, followed by 75 mg/day; $n = 1,752$) or placebo ($n = 1,739$), together with aspirin (150 - 325 mg loading dose followed by 75 - 162 mg/day), a fibrinolytic agent and, when appropriate, heparin for 48 hours. The patients were followed for 30 days.

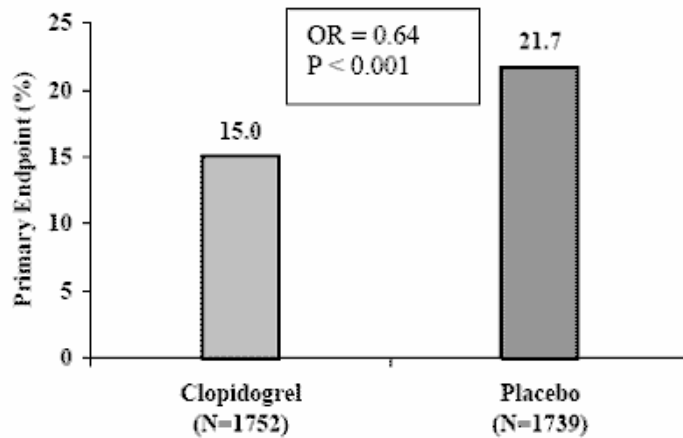
The primary endpoint was the occurrence of the composite of an occluded infarct related artery (defined as TIMI Flow Grade 0 or 1) on the pre-discharge angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography. For patients who did not undergo angiography, 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 pre-specified 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, 2 x 2 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 reinfarction, 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.

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 reinfarction, stroke or death by 9% (p = 0.002).

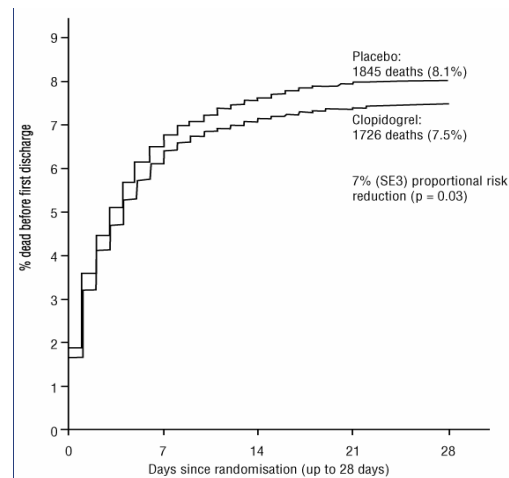
Outcome events in the COMMIT analysis

Event	Clopidogrel + aspirin n = 22,961	Placebo + aspirin n = 22,891	Odds ratio (95% CI)	p-value
Composite endpoint:				
Death, MI or stroke	2,121 (9.2%)	2,310 (10.1%)	0.91 (0.86, 0.97)	0.002
Death	1,726 (7.5%)	1,845 (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

COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial

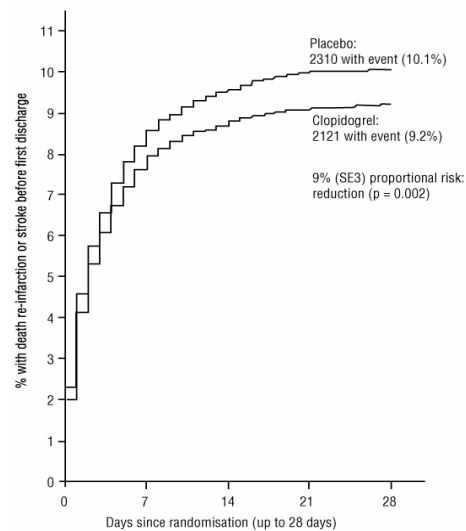
Note: 9 patients (2 clopidogrel and 7 placebo) suffered from both a non-fatal stroke and a non-fatal myocardial infarction (MI), hence the apparent disparity between composite endpoint and the sum of death, non-fatal MI and non-fatal stroke. Values for non-fatal MI and non-fatal stroke exclude patients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

Indications

Arrow - Clopidogrel is indicated for the prevention of vascular ischaemia associated with atherothrombotic events (myocardial infarction, stroke and vascular death) in patients with a history of symptomatic atherosclerotic disease.

Arrow - Clopidogrel is also indicated in combination with aspirin for patients with:

- unstable angina or non-ST elevation myocardial infarction. Clopidogrel 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 percutaneous coronary intervention, 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 is taken once a day, with or without food.

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

Adults

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

In patients with acute coronary syndrome (unstable angina or non-ST elevation myocardial infarction), clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued long-term at 75 mg once a day (with aspirin 75 - 325 mg daily).

In patients with ST-segment elevation acute myocardial infarction, clopidogrel treatment should be given as a single daily dose of 75 mg initiated with or without a 300 mg loading dose in combination with aspirin and with or without thrombolytics. Combined therapy should be started as early as possible after symptoms start. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting.

In patients who have had percutaneous coronary intervention with stent insertion, clopidogrel and aspirin should be continued for as long as is currently recommended in evidence based guidelines for the type of stent and circumstances of implantation or for as long as otherwise indicated, taking into account the overall atherothrombotic risk profile of the patient.

Elderly patients and patients with renal impairments

There are no data on the use of a 300 mg loading dose in elderly patients (aged 75 years or more) with ST-segment acute myocardial infarction, as no patients over 75 years old were included in the CLARITY study and no loading dose was used in the COMMIT study.

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

Arrow - Clopidogrel is contraindicated in the following conditions:

- with known hypersensitivity to clopidogrel or to any component of the product (see Further Information)
- severe hepatic impairment
- active pathological bleeding, e.g. peptic ulcer and intracranial haemorrhage
- breastfeeding (see Warnings and Precautions).

Warnings and Precautions

General

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 NSAIDs) should be used with caution in patients taking clopidogrel (see Interactions).
- 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.

Impaired renal function

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

Impaired hepatic function

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

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).

In the CAPRIE study, it was not mandatory to discontinue study medication in the case of an acute outcome event (acute myocardial infarction, ischaemic stroke or lower extremity amputation) and the patients had a favourable outcome as compared to the aspirin group.

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

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 neurological findings, renal dysfunction or fever. TTP is a 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 antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with aspirin, 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.

Carcinogenesis, mutagenesis, impairment of fertility

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 area under the curve (AUC) for the main circulating metabolite in elderly subjects).

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).

Clopidogrel was found to have no effect on the fertility of male and female rats at oral doses up to 400 mg/kg per day and was not teratogenic in rats (up to 500 mg/kg per day) and rabbits (up to 300 mg/kg per day).

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 500 mg and 300 mg/kg/day orally, 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 or operate machinery

No impairment of driving or psychometric performance was observed following clopidogrel administration.

Adverse Effects

Clopidogrel has been evaluated for safety in more than 42,000 patients, including 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.

Clopidogrel was well tolerated compared to aspirin in a large controlled clinical trial (CAPRIE). The overall tolerability of clopidogrel in this study was similar to aspirin, regardless of age, gender and race.

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 plus aspirin as compared to placebo plus aspirin, was not associated with an increase in life-threatening or fatal bleeds (event rates 2.2% versus 1.8% and 0.2% versus 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 plus aspirin versus 1.0% placebo plus aspirin), primarily gastrointestinal and at puncture sites, and minor bleeds (5.1% clopidogrel plus aspirin versus 2.4% placebo plus aspirin). The major bleeding event rate for clopidogrel plus aspirin was dose-dependent on aspirin (100 mg: 2.6%; 100 - 200 mg: 3.5%; 200 mg: 4.9%) as was the major bleeding event rate for placebo plus aspirin (< 100 mg: 2.0%; 100 - 200 mg: 2.3%; > 200 mg: 4.0%).

There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than 5 days prior to surgery (4.4% clopidogrel plus aspirin versus 5.3% placebo plus aspirin). In patients who remained on therapy within 5 days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus aspirin, and 6.3% for placebo plus aspirin.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus aspirin group (17.4%) versus the placebo plus aspirin group (12.9%), with the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in haemoglobin > 5 g/dL), being similar between groups (1.3 versus 1.1% in the clopidogrel plus aspirin and the placebo plus 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 plus aspirin and in the placebo plus 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 show in the table below.

Number of patients with bleeding events in COMMIT

Type of bleeding	Clopidogrel + aspirin (n = 22,961)	Placebo + aspirin (n = 22,891)	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

COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial

* 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 less than or equal to $30 \times 10^9/L$ 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, two 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 greater than or equal to 2.5% of patients on clopidogrel in the CAPRIE controlled clinical trial are shown in the following table 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 the events of 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-haemorrhagic adverse events was primarily due to the increase in rash seen in the clopidogrel group. There was no apparent difference between the two 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 and event(s)	CAPRIE		CURE	
	% Incidence (% discontinuation)		% Incidence (% discontinuation)	
	Clopidogrel n = 9,599	Aspirin n = 9,586	Clopidogrel + aspirin n = 6,259	Placebo + aspirin n = 6,303
<u>Body as a whole - general disorders</u>				
Chest pain	8.3 (0.2)	8.3 (0.3)	2.7 (0.02)	2.8 (0.0)
Accidental or 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)
<u>Cardiovascular disorders - general</u>				
Hypertension	4.3 (< 0.1)	5.1* (< 0.1)	0.9 (0.0)	0.9 (0.0)
<u>Central and peripheral nervous system disorders</u>				
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)
<u>Gastrointestinal</u>				
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)
<u>Metabolic and nutritional disorders</u>				
Hypercholesterolemia	4.0 (0)	4.4 (< 0.1)	0.1 (0.0)	0.2 (0.0)
<u>Musculoskeletal system disorders</u>				
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)
<u>Myo-, endo-, pericardial and valve disorders</u>				

Body system and event(s)	CAPRIE		CURE	
	% Incidence (% discontinuation)		% Incidence (% discontinuation)	
	Clopidogrel n = 9,599	Aspirin n = 9,586	Clopidogrel + aspirin n = 6,259	Placebo + aspirin n = 6,303
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)
<u>Platelet, bleeding and clotting disorders</u>				
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)
<u>Psychiatric disorders</u>				
Depression	3.6 (0.1)	3.9 (0.2)	0.7 (0.02)	0.7 (0.0)
<u>Resistance mechanism disorders</u>				
Infection	4.7 (< 0.1)	4.2 (0.1)	1.3 (0.0)	1.2 (0.0)
<u>Respiratory system disorders</u>				
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)
<u>Skin and appendage disorders</u>				
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)
<u>Urinary system disorders</u>				
Urinary tract infection	3.1 (0)	3.5 (0.1)	1.5 (0.0)	1.4 (0.0)
<u>Vascular (extra-cardiac) disorders</u>				
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)

* 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 greater than or equal to 0.1% as well as all serious and clinically relevant adverse reactions are listed below according to the World Health Organisation classification.

Their frequency is defined using the following conventions: common $\geq 1/100$ (1%) and $< 1/10$ (10%), uncommon $\geq 1/1,000$ (0.1%) and $< 1/100$ (1%), and rare $\geq 1/10,000$ (0.01%) and $< 1/1,000$ (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 reticulo-endothelial system disorders

Uncommon: leucopenia and eosinophilia

Post-marketing experience

The following have been reported spontaneously from worldwide post-marketing experience: very common $\geq 1/10$ ($\geq 10\%$), common $\geq 1/100$ (1%) and $< 1/10$ (10%), uncommon $\geq 1/1,000$ (0.1%) and $< 1/100$ (1%), and rare $\geq 1/10,000$ (0.01%) and $< 1/1,000$ (0.1%), and 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

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

Very rare:

- serious cases of bleeding, mainly skin, musculoskeletal (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 in patients taking clopidogrel concomitantly with aspirin or clopidogrel with aspirin and heparin (see Interactions)
- thrombotic thrombocytopenic purpura (TTP)

- aplastic anaemia, neutropenia, pancytopenia, agranulocytosis, granulocytopenia, anaemia

Skin and subcutaneous tissue disorders

Very rare: maculopapular 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

Very rare: fever, syncope

Interactions

Aspirin

A pharmacodynamic interaction between clopidogrel and aspirin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and aspirin have been administered together for up to 1 year (see also Warnings and Precautions - General).

Injectable anticoagulants

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

Glycoprotein IIb/IIIa inhibitors

As a pharmacological interaction between clopidogrel and glycoprotein IIb/IIIa inhibitors is possible, concomitant use should be undertaken with caution.

Thrombolytics

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparins are co-administered with aspirin. However, the use of clopidogrel with thrombolytic agents should be undertaken with caution.

Oral anticoagulants (including warfarin)

Clopidogrel inhibits platelet aggregation, so patients receiving both clopidogrel and warfarin may be at an increased risk of bleeding. Concomitant administration of warfarin and clopidogrel 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. Consequently, there is a potential increased risk of gastrointestinal bleeding and NSAIDs and clopidogrel should be co-administered with caution (see Warnings and Precautions).

Drugs metabolised by cytochrome P450 2C9

At high concentrations *in vitro*, clopidogrel inhibits cytochrome P450 2C9. Accordingly, clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, fluvastatin, and many NSAIDs, 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 clopidogrel.

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.

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 (phenobarbitone), cimetidine or oestrogen.

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

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

Overdosage

In animals, clopidogrel at single oral doses greater than or equal to 1,500 mg/kg caused necrotic haemorrhagic gastritis, oesophagitis and enteritis in mice, rats and baboons. Necrotic tubulopathy and tubulointerstitial 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.

Pharmaceutical Precautions

Shelf-life: 2 years

Storage: Store at or below 25 °C

Medicine Classification

Prescription Medicine

Package Quantities

Blister packs of 28 tablets

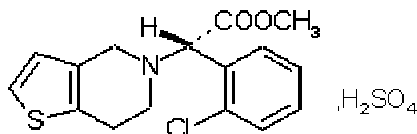
Bottles of 28, 90, 500 and 1000 tablets

Not all pack sizes or pack types may be marketed.

Further Information

Arrow - Clopidogrel contains clopidogrel hydrogen sulfate, which 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°.

The chemical name for clopidogrel hydrogen sulfate is methyl (+)-(S)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c] pyridine-5(4H)-acetate sulfate (1:1). The structural formula of clopidogrel is:



$C_{16}H_{16}ClNO_2S.H_2SO_4$ Molecular weight: 419.9

CAS: 120202-66-6 (clopidogrel hydrogen sulfate), 113665-84-2 (clopidogrel base)

Arrow - Clopidogrel tablets also contain the following excipients: propylene glycol (macrogol 6000), mannitol, microcrystalline cellulose, low substituted hydroxypropylcellulose, hydrogenated vegetable oil and Opadry white OY-LS-28908 (contains lactose). The tablets are gluten free.

Name and Address

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Date of Preparation

23 July 2009