

AUSTRALIAN PRODUCT INFORMATION – CLOPIDOGREL-WINTHROP® (CLOPIDOGREL HYDROGEN SULFATE) FILM COATED TABLET

1 NAME OF THE MEDICINE

Clopidogrel hydrogen sulfate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clopidogrel Winthrop 75 mg contains 97.875 mg of clopidogrel hydrogen sulfate which is the molar equivalent of 75 mg of clopidogrel base.

Excipient with known effect: the coating contains lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

75 mg film coated tablets - pink round slightly biconvex film coated tablets, engraved “75” on one side and “1171” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

Acute Coronary Syndrome

Clopidogrel Winthrop is indicated in combination with aspirin for patients with:

- Unstable angina or non-ST-elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death or refractory ischaemia). Clopidogrel Winthrop 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, Clopidogrel Winthrop 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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 mg-325 mg daily).
- 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. 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.

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.

No dosage adjustment is necessary for either elderly patients or patients with renal impairment. (see Section 5.2 Pharmacokinetic properties).

Pharmacogenetics

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolisers increases antiplatelet response (see Section 5.2 Pharmacokinetic properties, Excretion, Pharmacogenetics), an appropriate dose regimen for this patient population has not been established in clinical outcome trials. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolisers.

Children and Adolescents

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to clopidogrel or any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.

- Breast-feeding (see Section 4.6 Fertility, pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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, and in patients receiving treatment with acetylsalicylic acid, heparin, glycoprotein IIb/IIIa inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers. Due to the increased risk of hemorrhage, triple antiplatelet therapy (clopidogrel + aspirin + dipyridamole) for stroke secondary prevention is not recommended in patients with acute non-cardioembolic ischemic stroke or TIA (see Section 4.5 Interactions with other medicines and other forms of interactions).

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), Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). 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 Section 4.5 Interactions with other medicines and other forms of 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.

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

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 Section 4.8 Adverse effects (Undesirable effects)).

Pharmacogenetics

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is mainly due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 and by concomitant medications that interfere with CYP2C19. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite. In patients who are CYP2C19 poor metabolisers clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. (see Section 5.1 Pharmacodynamic properties, Clinical trials and Section 5.2 Pharmacokinetic properties, Excretion, Pharmacogenetics).

Use of drugs that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see Section 4.5 Interactions with other medicines and other forms of interactions).

Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Although a higher dose regimen in poor metabolisers increases antiplatelet response (see Section 5.2 Pharmacokinetic properties, Excretion, Pharmacogenetics), an appropriate dose regimen for this patient population has not been established in clinical outcome trials. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolisers (see Section 4.2 Dose and method of administration, Pharmacogenetics).

CYP2C19 Metabolism

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g. omeprazole) should be discouraged (see Section 5.2 Pharmacokinetic properties, Excretion, Pharmacogenetics and Section 4.4 Special warnings and precautions for use). If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole.

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

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 Section 4.8 Adverse effects (Undesirable 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. Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel is not recommended.

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.

Acquired Haemophilia

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists and clopidogrel should be discontinued.

Cross-reactivity among thienopyridines

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see Section 4.8 Adverse effects (Undesirable effects)). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological reactions such as thrombocytopenia and neutropenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for cross-reactivity is advised.

Use in hepatic impairment

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 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).

Use in renal impairment

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

Use in the elderly

No data available

Paediatric use

See Section 4.2 Dose and method of administration, Children and Adolescents.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 one year. See also Section 4.4 Special warnings and precautions for use, – General.

Oral Anticoagulants (including warfarin)

The concomitant administration of Clopidogrel Winthrop with warfarin is not recommended since it may increase the intensity of bleeding.

Glycoprotein IIb/IIIa inhibitors

Clopidogrel Winthrop 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.

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.

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

The effects of Clopidogrel Winthrop 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 heparins are co-administered with aspirin. The safety of concomitant administration of Clopidogrel Winthrop with thrombolytic agents has not been formally established and should be undertaken with caution.

Drugs associated with bleeding risk

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of drugs associated with bleeding risk should be undertaken with caution (see Section 4.4 Special warnings and precautions for use).

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, there is a potential increased risk of gastrointestinal bleeding and NSAIDs and clopidogrel should be co-administered with caution (see Section 4.4 Special warnings and precautions for use).

Selective Serotonin Reuptake Inhibitors (SSRIs):

Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Drugs metabolised by Cytochrome P450 2C9

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

Other concomitant therapy

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel.

Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see Section 4.4 Special warnings and precautions for use).

Inhibitors of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole) should be discouraged (see Section 5.2 Pharmacokinetic properties, Excretion, Pharmacogenetics and Section 4.4 Special warnings and precautions for use). If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole.

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

Proton Pump Inhibitors (PPI): In a crossover clinical study (N=72 healthy subjects), clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. Mean maximal platelet aggregation intensity % (MAI) was the primary pharmacodynamic endpoint of the clinical study and was used in the calculation of the mean inhibition of platelet aggregation % (IPA). Similar trends in results were seen across both the MAI% and IPA%. The exposure to the active metabolite of clopidogrel was decreased by 45% (Day 1) and 40% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation with 5 µM ADP was diminished by 39% (24 hours) and 21% (Day 5) when clopidogrel and omeprazole were administered together. The same results were observed when omeprazole 80mg was administered 12 hours apart.

In a crossover clinical study (N=66), healthy subjects were administered clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days. Mean maximal platelet aggregation intensity % was the primary pharmacodynamic endpoint of the clinical study and was used in the calculation of the mean inhibition of platelet aggregation %. Similar trends in results were seen across both the MAI% and IPA%. The exposure to the active metabolite of clopidogrel was decreased by 20% (Day 1) and 14% (Day 5) when clopidogrel and pantoprazole were administered together. Mean inhibition of platelet aggregation was diminished by 15% (24 hours) and 11% (Day 5) when clopidogrel and pantoprazole were administered together. These results indicate that clopidogrel can be administered with pantoprazole.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies.

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, or oestrogen.

In a study comparing administration of warfarin with either clopidogrel (N=20) or placebo (N=23) the administration of clopidogrel 75 mg/day for 8 days did not modify the

pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy (at least 2 months). Coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis. However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9. It is unlikely that clopidogrel interferes with the metabolism of drugs such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

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

CYP2C8 substrate drugs:

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

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, anti-diabetic agents (including insulin), anti-epileptic agents, GPIIb/IIIa antagonists and hormone replacement therapy without evidence of clinically significant adverse interactions.

As with other oral P2Y₁₂ inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

Rosuvastatin

Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold (C_{max}) after administration of a 300 mg clopidogrel dose, and by 1.4-fold (AUC) without effect on C_{max} after repeated administration of a 75 mg clopidogrel dose.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 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 – Pregnancy Category B1

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 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 Section 4.3 Contraindications).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Studies Experience

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, there was a significant difference between the two treatment groups for 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 (<100 mg: 2.6%; 100-200 mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo + aspirin (<100 mg: 2.0%; 100-200 mg: 2.3%; >200 mg: 4.0%).

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 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, there was an overall increase in bleeding in the clopidogrel + aspirin group (17.4%) versus the placebo + 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 + 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 major bleeding in COMMIT was low and similar in both groups, as show in Table 1 below.

Table 1 - 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

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

In CHARISMA, a study conducted in a broad patient population including patients with prior documented coronary artery disease, cerebrovascular disease or peripheral arterial disease as well as patients with a combination of atherothrombotic risk factors only, all receiving a background therapy with low dose aspirin (75-162 mg), there was an excess in moderate and severe bleeding, as adjudicated to the GUSTO definitions, in the clopidogrel group. This represented a number needed to treat, to harm, of 84 in 23 months of follow-up.

Table 2

Type of bleeding (GUSTO)	Number (%) with event		Difference Clopidogrel – Placebo (%) (95% CI)
	Clopidogrel + aspirin (N=7802)	Placebo + aspirin (N=7801)	
Any	2827 (36.2)	1616 (20.7)	15.52 (14.12, 16.91)
Severe/moderate	290 (3.7)	197 (2.5)	1.19 (0.65, 1.74)

*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 $<30 \times 10^9/L$ have been reported.

Aplastic anaemia has occurred whilst on clopidogrel treatment.

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-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).

Table 3 - 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)

	CAPRIE		CURE	
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				
Hypercholesterolaemia	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)
Pruritis	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≤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 ≥ 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: > 1/100 (1%) and < 1/10 (10%);

uncommon: ≥ 1/1000 (0.1%) and < 1/100 (1%) and

rare: ≥ 1/10000 (0.01%) and < 1/1000 (0.1%).

Central and peripheral nervous system disorders

uncommon: Paraesthesia, headache, dizziness

rare: Vertigo

Gastrointestinal system disorders

common: Dyspepsia, abdominal pain, diarrhea

uncommon: Flatulence, nausea, gastritis, constipation, vomiting, gastric, peptic or duodenal ulcer

Platelet, bleeding and clotting disorders

uncommon: Bleeding time increased, platelets decreased

Skin and appendages disorders

uncommon: Rash, pruritis

White cell and RES disorders

uncommon: Leucopenia, neutrophils decreased and eosinophilia

Post-Marketing Experience

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

Note	<i>very common</i>	≥ 1/10 (≥ 10%)
	<i>common</i>	≥ 1/100 and < 1/10 (≥ 1% and < 10%)
	<i>uncommon</i>	≥ 1/1000 and < 1/100 (≥ 0.1% and < 1.0%)
	<i>rare</i>	≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
	<i>very rare</i>	< 1/10,000 (< 0.01%)
	<i>Not known</i>	cannot be estimated from available data

Musculoskeletal, connective and bone

very rare: Arthralgia, arthritis, myalgia

Immune system disorders

very rare: anaphylactoid reactions, serum sickness

uncommon: cross-reactive hypersensitivity among thienopyridine (such as ticlopidine, prasugrel) (see Section 4.4 Special warnings and precautions for use)

Not known: Insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)

Cardiac disorders

Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel

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 Section 4.5 Interactions with other medicines and other forms of interactions)

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

Very rare cases of acquired haemophilia A have been reported.

very rare: aplastic anaemia, neutropenia, pancytopenia, agranulocytosis, granulocytopenia, anaemia

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

Skin and Subcutaneous tissue disorders

very rare: maculopapular, erythematous or exfoliative rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP)), drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), eczema, lichen planus

Psychiatric

very rare: confusion, hallucinations

Nervous System disorders

very rare: taste disturbances

Not known: ageusia

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, eosinophilic pneumonia

Renal and Urinary disorders

very rare: glomerulopathy

Reproductive systems and breast disorders

very rare: gynaecomastia

Investigations

very rare: blood creatinine increase, abnormal liver function tests

General disorders and administration site conditions

very rare: fever, syncope

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis. The active metabolite of clopidogrel selectively inhibits the binding of ADP to its platelet P2Y₁₂ receptor and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Due to the irreversible binding, platelets exposed 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.

Clinical trials

The safety and efficacy of clopidogrel in preventing vascular ischaemic events has been evaluated in four double-blind studies: the CAPRIE study, a comparison of clopidogrel to aspirin, and the CURE, CLARITY and COMMIT 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.

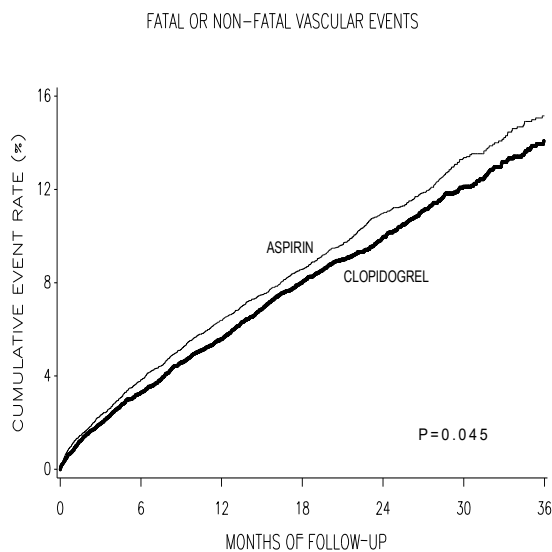
Table 4 - Outcome Events of the Primary Analysis

	Clopidogrel	Aspirin
Patients	9599	9586
IS (fatal or not)	438 (4.56%)	461 (4.81%)
MI (fatal or not)	275 (2.86%)	333 (3.47%)
Other vascular death	226 (2.35%)	226 (2.36%)
Total	939 (9.78%)	1020 (10.64%)

As shown in Table 4 above, clopidogrel was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.78% vs. 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 showing the overall event rate are shown in the Figure 1 below. The event curves separated early and continued to diverge over the 3-year follow-up period.

Figure 1



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, $n = 6244$) 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 ischaemia) 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 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 table below, mainly related to a reduction in occluded infarct-related arteries.

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.

Table 5 - Event Rates for the Primary Composite Endpoint in the CLARITY Study

	Clopidogrel + aspirin N = 1753	Placebo + aspirin N = 1739	OR	95% CI
Number (%) of patients reporting the composite endpoint	262 (15.0%)	377 (21.7%)	0.64	0.53, 0.76
Occluded IRA				
N (subjects undergoing angiography)	1640	1634		
n (%) patients reporting endpoint	192 (11.7%)	301 (18.4%)	0.59	0.48, 0.72
Death				
n (%) patients reporting endpoint	45 (2.6%)	38 (2.2%)	1.18	0.76, 1.83
Recurrent MI				
n (%) patients reporting endpoint	44 (2.5%)	62 (3.6%)	0.69	0.47, 1.02

The total number of patients with a component event (occluded IRA, death or recurrent MI) is greater than the number of patients with a composite event because some patients had more than a single type of component event.

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).

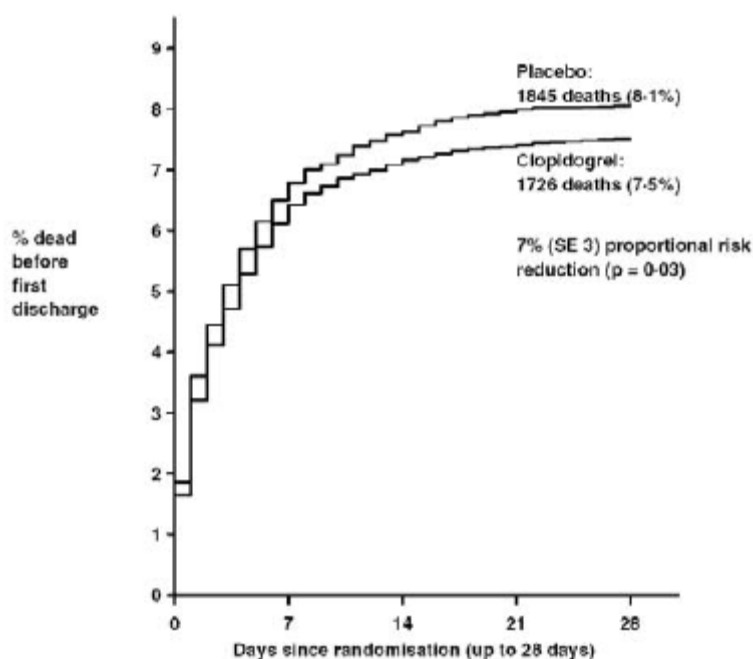
As shown in Table 6 and Figure 2 and Figure 3 below, clopidogrel significantly reduced the relative risk of death from any cause by 7% ($p = 0.029$) and the relative risk of the combination of re-infarction, stroke or death by 9% ($p = 0.002$), representing an absolute risk reduction of 5 and 9 patients per 1000 treated (0.5 and 0.9%), respectively.

Table 6 - 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

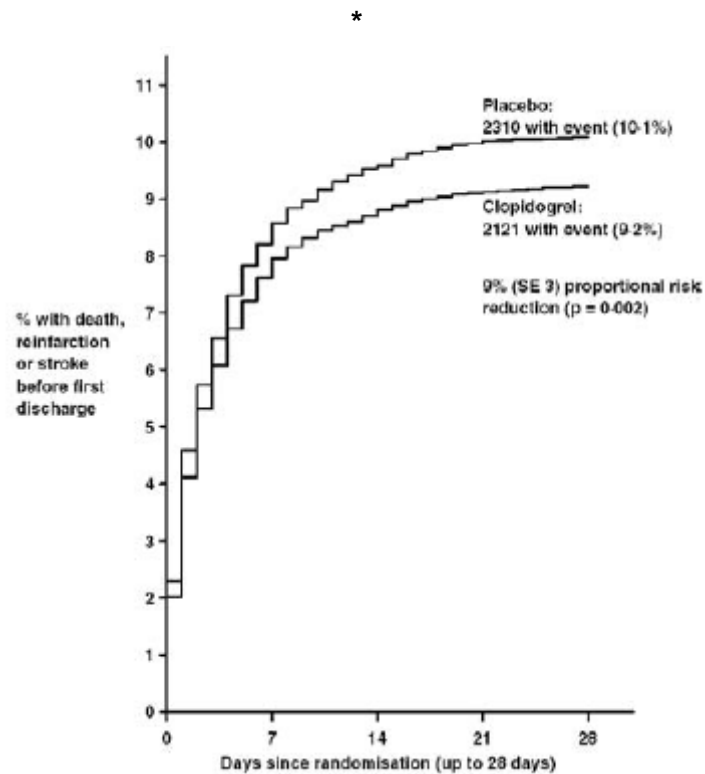
Note: 9 patients (2 clopidogrel and 7 placebo) suffered from both a non-fatal stroke and a non-fatal MI, hence the apparent disparity between composite endpoint and the sum of death, non-fatal MI and non-fatal stroke. Values for non-fatal MI and non-fatal stroke exclude patients who died of any cause.

Figure 2 - Cumulative Event Rates for Death in the COMMIT Study



* All treated patients received aspirin.

Figure 3 - 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After single and repeated oral doses of 75 mg/day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/mL after a single 75mg oral dose) occurred approximately 45 minutes after dosing. The increase in area under the curve (AUC) in the range of 75 to 300 mg is dose proportional, while the C_{max} increases by 3-fold for a 4-fold increase in dose. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Metabolism

Clopidogrel is extensively metabolised by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including

CYP3A4, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

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

Distribution

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.

Excretion

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. After a single, oral dose of 75 mg, clopidogrel has a half life of approximately 6 hours. The half life of the active metabolite is about 30 minutes.

Pharmacogenetics *

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and *3 alleles are nonfunctional. CYP2C19*2 and *3 account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metaboliser genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese and are listed in Table 7 below. Tests are available to determine a patient's CYP2C19 genotype.

Table 7 - CYP2C19 Phenotype and Genotype Frequency

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

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μ M ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials (see Section 4.2 Dose and method of administration).

Table 8 - Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metaboliser Status

	Dose	Ultrarapid (n=10)	Extensive (n=10)	Intermediate (n=10)	Poor (n=10)
AUClast (ng.h/mL)	300 mg (Day 1)	33 (11)	39 (24)	31 (14)	14 (6)
	600 mg (Day 1)	56 (22)	70 (46)	56 (27)	23 (7)
	75 mg (Day 5)	11 (5)	12 (6)	9.9 (4)	3.2 (1)
	150 mg (Day 5)	18 (8)	19 (8)	16 (7)	7 (2)
IPA (%) ^{0*}	300 mg (24 h)	40 (21)	39 (28)	37 (21)	24 (26)
	600 mg (24 h)	51 (28)	49 (23)	56 (22)	32 (25)
	75 mg (Day 5)	56 (13)	58 (19)	60 (18)	37 (23)
	150 mg (Day 5)	68 (18)	73 (9)	74 (14)	61 (14)

Values are mean (SD)

* Inhibition of platelet aggregation with 5 μ M ADP; larger value indicates greater platelet inhibition

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 μ M ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have, however, been a number of retrospective analyses to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), and TRITON-TIMI 38 (n=1477) and ACTIVE-A (n=601), as well as a number of published cohort studies.

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

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

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

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

Special Populations

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

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.

Renal Impairment

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. 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

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.

Ethnicity *

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Section 5.2 Pharmacokinetic properties,

Excretion, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

5.3 PRECLINICAL SAFETY DATA

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).

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).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet contains mannitol, macrogol 6000, microcrystalline cellulose, hydrogenated castor oil, hypolose, carnauba wax, OPADRY II complete film coating system 32K14834 Pink (coating contains lactose monohydrate).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Clopidogrel Winthrop 75 mg is available in blister packs (PVC/PVDC/Al) containing 28 tablets.

Clopidogrel Winthrop is a registered trademark of sanofi-aventis.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

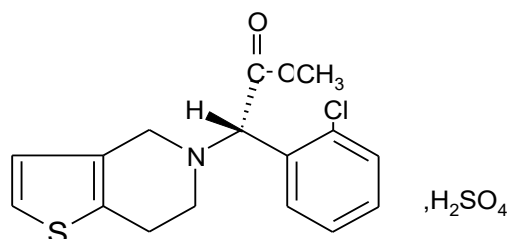
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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°.

Chemical structure

Clopidogrel hydrogen sulfate has the following chemical structure:



Molecular Formula: C₁₆H₁₆ClNO₂S.H₂SO₄

Molecular Weight: 419.9.

Chemical Name: methyl (+)-(S)- α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4H)-acetate sulfate (1:1)

CAS number

120202-66-6 (Clopidogrel hydrogen sulfate),

113 665-84-2 (Clopidogrel base)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

29 June 2001

10 DATE OF REVISION

23 April 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor address updated