NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Arrow – Clopid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains clopidogrel hydrogen sulfate equivalent to clopidogrel 75 mg.

Excipient with known effect: lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Pink, circular, biconvex, film-coated tablet debossed "L 11" on one side of the tablet and plain on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Prevention of vascular ischaemia associated with atherothrombotic events (MI, stroke and vascular death) in patients with a history of symptomatic atherosclerotic disease.

Acute Coronary Syndrome
Arrow-Clopid is indicated in combination with aspirin for patients with:

- Unstable angina or non-ST elevation MI. Arrow-Clopid is indicated for early and long-term reduction of atherothrombotic events (myocardial infarction, stroke, vascular death and refractory ischaemia) whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).
- ST-segment elevation acute myocardial infarction. In this population, clopidogrel has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke.

4.2 Dose and method of administration
Dose
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 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.

Special Populations
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 5.1 Pharmacodynamic properties; 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.

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

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

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), or selective serotonin reuptake inhibitors (SSRIs) 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), 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 Interaction with other medicines and other forms of interaction).
- 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.

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).

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 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; Pharmacogenetics and Clinical Efficacy and Safety; Pharmacogenetics). 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 5.1 Pharmacodynamic properties; 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).

CYP2C8 substrates
Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicines (see section 4.5 Interaction with other medicines and other forms of interaction).

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 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 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 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, 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 allergic cross-reactivity among thienopyridines has been reported (see section 4.8 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.

4.5 Interaction with other medicines and other forms of interaction

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 section 4.4 Special warnings and precautions for use).

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 other thrombolytic agents 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.

Oral anticoagulants
Due to the increased risk of bleeding, concomitant administration of oral anticoagulants (warfarin, dabigatran, rivaroxaban and apixaban) 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 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 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
Clopidogrel is metabolised to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition, the clinical relevance of this interaction is uncertain. Avoid concomitant use of strong or moderate CYP2C19 inhibitors, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine. (see section 5.1 Pharmacodynamic properties; 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.

Studies of specific drug interactions yielded the following results:

Proton Pump Inhibitors (PPI): In a crossover clinical study, 72 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together.

In a second study 72 healthy subjects were given the same doses of clopidogrel and omeprazole but the drugs were administered 12 hours apart from the clopidogrel standard regimen; the results were similar indicating that administering clopidogrel and omeprazole at different times does not prevent their interaction, that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19.

In a third interaction study with omeprazole 80 mg administered with a higher dose regimen of clopidogrel (600-mg loading dose followed by 150 mg/day), a degree of interaction was observed similar to that noted in the other omeprazole interaction studies. However, active metabolite formation and platelet aggregation were at the same level as clopidogrel administered alone at the standard dose regimen.

In a crossover clinical study, 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. 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.

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.

Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on haemostasis. 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.

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.

CYP2C8 substrate medicinal products
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, selexipag) should be undertaken with caution.

4.6 Fertility, pregnancy and lactation

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 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).

Fertility
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).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable 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. The clinically relevant adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

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

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

The overall incidence of other bleeding disorders was higher in the clopidogrel group compared to aspirin. However, the incidence of severe events was similar in both treatment groups. The most frequent events reported were purpura/bruising and epistaxis. Other less frequently reported events were haematoma, haematuria and eye bleeding (mainly conjunctival).

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

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

* 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 x 10^9/L have been reported.

Aplastic anaemia has occurred whilst on clopidogrel treatment.

Severe neutropenia (< 0.45 x 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 ≥ 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 the 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 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 ≥ 2.5% of patients receiving clopidogrel in CAPRIE and CURE

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

Musculoskeletal system disorders				
Arthralgia	6.3 (0.1)	6.2 (0.1)	0.9 (0.0)	0.9 (0.0)
Back pain	5.8 (0.1)	5.3 (< 0.1)	1.0 (0.03)	1.2 (0.0)
Myo-, endo-, pericardial and valve disorders				
Angina pectoris	10.1 (0.6)	10.7 (0.4)	0.1 (0.0)	0.1 (0.0)
Coronary artery disorder	6.2 (0.3)	5.6 (0.3)	0.03 (0.0)	0.06 (0.0)
Platelet, bleeding and clotting disorders				
Purpura	5.3* (0.3)	3.7 (0.1)	0.3 (0.0)	0.1 (0.0)
Epistaxis	2.9 (0.2)	2.5 (0.1)	0.2 (0.08)	0.1 (0.02)
Psychiatric disorders				
Depression	3.6 (0.1)	3.9 (0.2)	0.7 (0.02)	0.7 (0.0)
Resistance mechanism disorders				
Infection	4.7 (< 0.1)	4.2 (0.1)	1.3 (0.0)	1.2 (0.0)
Respiratory system disorders				
Upper respiratory tract infection	8.7 (< 0.1)	8.3 (< 0.1)	1.1 (0.0)	1.0 (0.0)
Dyspnoea	4.5 (0.1)	4.2. (0.1)	1.9 (0.0)	1.9 (0.02)
Rhinitis	4.2 (0.1)	4.2 (< 0.1)	0.2 (0.0)	0.1 (0.0)
Bronchitis	3.7 (0.1)	3.7 (0)	1.1 (0.0)	1.5 (0.0)
Coughing	3.1 (< 0.1)	2.7 (< 0.1)	1.3 (0.0)	1.2 (0.0)
Skin and appendage disorders				
Rash	4.2* (0.5)	3.5 (0.2)	1.3 (0.29)	1.1 (0.14)
Pruritus	3.3* (0.3)	1.6 (0.1)	0.5 (0.11)	0.5 (0.05)
Urinary system disorders				
Urinary tract infection	3.1 (0)	3.5 (0.1)	1.5 (0.0)	1.4 (0.0)
Vascular (extra-cardiac) 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)

* 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 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%)
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, diarrhoea
Uncommon: flatulence, nausea, gastritis, constipation, vomiting, gastric, peptic or duodenal ulcer

Skin and appendages disorders
Uncommon: rash, pruritis

Platelet, bleeding and clotting disorders
Uncommon: bleeding time increased, platelets decreased

White cell and reticulo-endothelial system disorders
Uncommon: leucopenia, neutrophils decreased and eosinophilia

Post-marketing experience

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

System organ class	**Frequency and symptom**
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 section 4.5 Interaction with other medicines and other forms of interaction). Thrombotic thrombocytopenic purpura (TTP), acquired haemophilia A, agranulocytosis, aplastic anaemia, neutropenia, pancytopenia, granulocytopenia, anaemia.
Immune system disorders	*unknown*: cross-reactive hypersensitivity among thienopyridine (such as ticlopidine, prasugrel) (see section 4.4 Special warnings and precautions for use) *very rare*: anaphylactoid reactions, serum sickness *not known:* Insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)
Psychiatric disorders	*very rare*: confusion, hallucinations
Nervous system disorders	*very rare*: taste disturbances *not known:* ageusia
Cardiac disorders	*not known:* Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel
Vascular disorders	*very rare*: vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	*very rare*: bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders	*very rare*: colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
Hepatobiliary disorders	*very rare*: hepatitis, acute liver failure
Skin and subcutaneous tissue disorders	*very rare*: maculopapular or erythematous 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
Musculoskeletal and connective tissue disorders	*very rare*: arthralgia, arthritis, myalgia

Renal and urinary disorders	*very rare*: glomerulopathy
Reproductive system and breast disorders	*very rare:* gynaecomastia
General disorders and administration site conditions	*very rare*: fever, syncope
Investigations	*very rare*: blood creatinine increase, abnormal liver function tests

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (https://nzphvc.otago.ac.nz/reporting/).

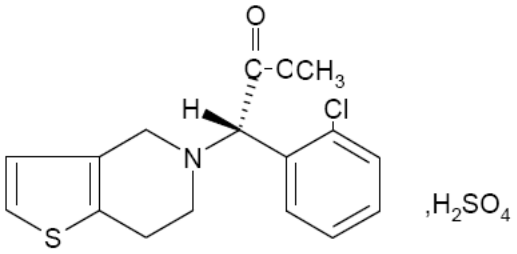
4.9 Overdose
In animals, clopidogrel at single oral doses greater than or equal to 1500 mg/kg caused necrotic haemorrhagic gastritis, oesophagitis and enteritis in mice, rats and baboons. Necrotic tubulopathy and tubulointerstitial nephritis were also noted in mice.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antithrombotic agents, Platelet aggregation inhibitors; ATC code: B01AC04

Clopidogrel hydrogen sulfate has the following chemical structure:



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

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

CAS Number: 120202-66-6 (Clopidogrel hydrogen sulfate),

113 665-84-2 (Clopidogrel base).

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

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.

Metabolism

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 adenosine diphosphate (ADP) to its platelet 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.

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.

CLINICAL EFFICACY AND SAFETY

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.

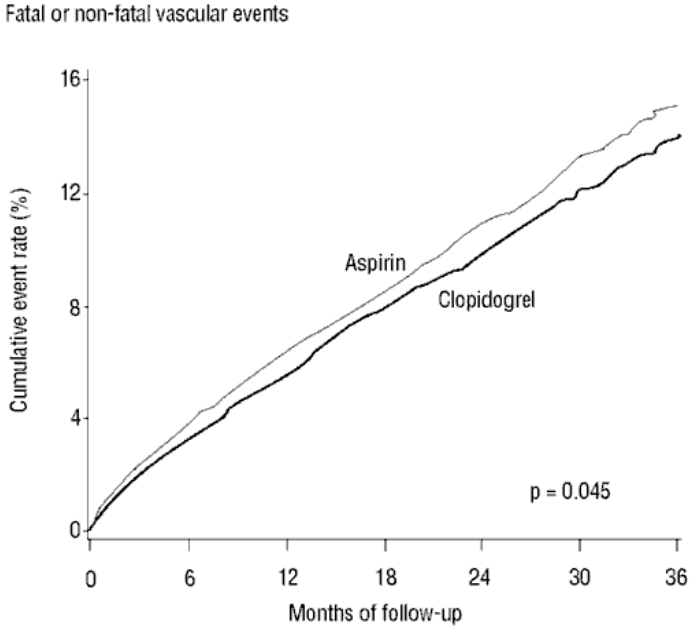
The trial's primary outcome was the time to first occurrence of new ischaemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

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 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 to 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 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 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 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 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 to162 mg/day; n = 1,752) or placebo (n = 1,739), 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.

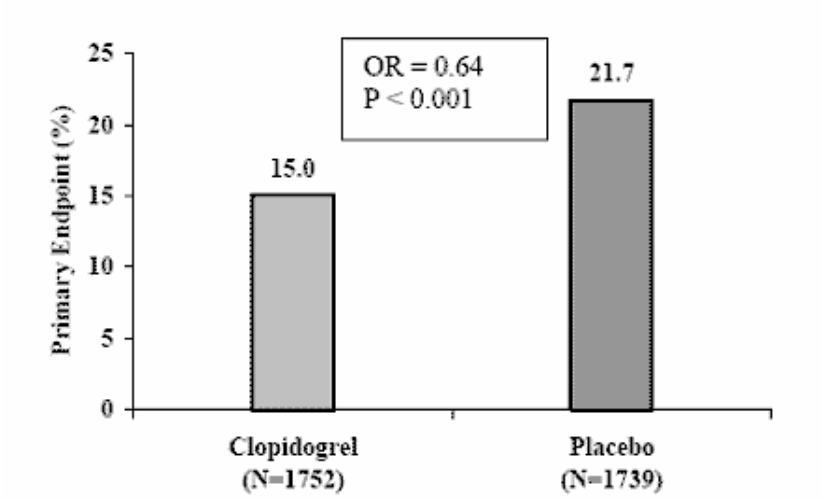
The primary endpoint was the occurrence of the composite of an occluded infarct related artery (defined as TIMI Flow Grade 0 or 1) on the pre-discharge angiogram, or death or recurrent myocardial infarction by the time of the start of coronary angiography. For patients who did not undergo angiography,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

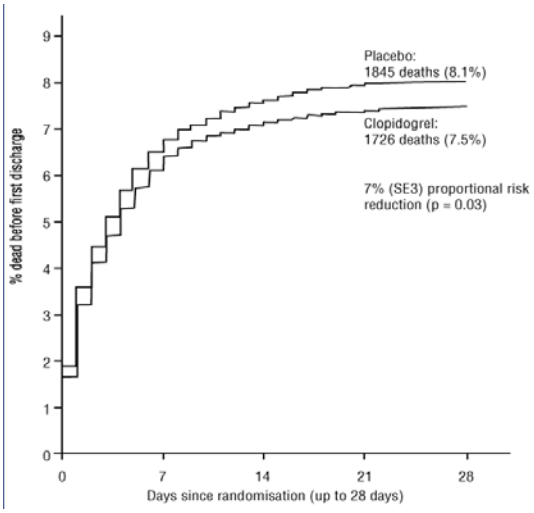
As shown in the table and figures below, clopidogrel significantly reduced the relative risk of death from any cause by 7% (p = 0.029) and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002).

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

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.

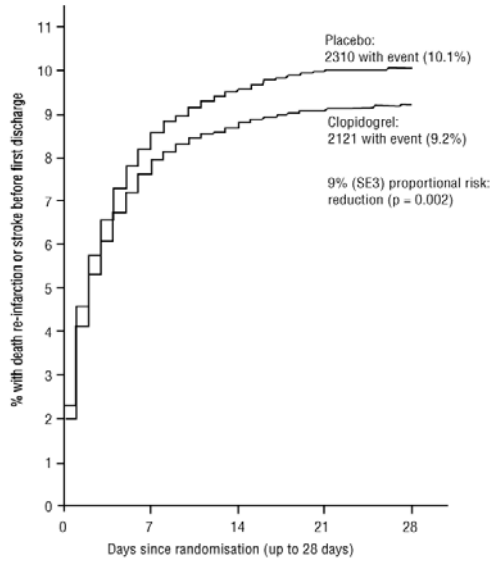
Cumulative event rates for death in the COMMIT study*



* 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.

Pharmacogenetics

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomized, 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. Such studies have included CHARISMA (n=2428) and TRITON-TIMI 38 (n=1477), as well as a number of published cohort studies.

In TRITON-TIMI 38 and three 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 the study by Trenk et al. the *2 allele variant of CYP2C19 was associated with high platelet reactivity in patients on clopidogrel and this high platelet reactivity was in turn associated with increased risks of death and MI in the first year after elective stent replacement.

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

5.2 Pharmacokinetic properties

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/mL after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. 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 metabolized 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. This metabolic pathway is mediated by CYP2C19, 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 ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120 hour interval after dosing. After a single, oral dose of 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 metabolizers. 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 metabolizer status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for whites,

4% for blacks and 14% for Chinese and are listed in the table below. Tests are available to determine a patient's CYP2C19 genotype.

CYP2C19 Phenotype and Genotype Frequency

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

A crossover study in 40 healthy 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 μM ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in 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).

Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metaboliser Status

	DOSE	**ULTRARAPID (N=10)**	**EXTENSIVE (N=10)**	**INTERMEDIATE (N=10)**	**POOR (N=10)**
AUC_{last} (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 (%)a*	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)

a* Inhibition of platelet aggregation with 5μM ADP; larger value indicates greater platelet inhibition

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomized, 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. Such studies have included CHARISMA (n=2428) and TRITON-TIMI 38 (n=1477), as well as a number of published cohort studies.

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.

Renally Impaired Patients
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 (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 5.1 Pharmacodynamic properties; 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
Carcinogenicity and mutagenicity
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 ≈ 18 times the anticipated patient exposure, based on plasma 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).

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate, low substituted hydroxypropyl cellulose, silica colloidal anhydrous, castor oil hydrogenated, dimeticone, purified water, InstaCoat Universal (Pink A05G30176).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 25°C.

6.5 Nature and contents of container
Aluminium foil/foil blister strips. Pack size of 28 and 84 tablets.

Not all pack types or pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR
Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL
7 February 2013

10. DATE OF REVISION OF THE TEXT
15 February 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Warning regarding patients treated concomitantly with clopidogrel and CYP2C8 substrate medicines as per Medsafe request.
4.5	Interaction with CYP 2C8 substate drugs updated to include selexipag as per Medsafe request.