

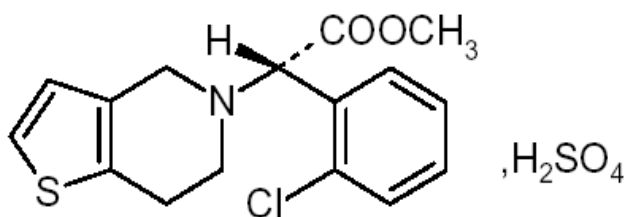
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Clopidogrel hydrogen sulfate

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

Structural formula:



Molecular formula: $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ Molecular weight: 419.9

CAS Registry no.: 120202-66-6 (Clopidogrel hydrogen sulfate), 113 665-84-2 (Clopidogrel base).

DESCRIPTION

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°.

Each film-coated tablet contains magnesium stearate, sodium lauryl sulfate, silica – colloidal anhydrous, cellulose – microcrystalline, lactose anhydrous and croscarmellose sodium. The coating contains Opadry II complete film coating system 40C18303 White (Proprietary Ingredient Number 13191) and Opadry complete film coating system YS-1-7006 Clear (Proprietary Ingredient Number 12789).

PHARMACOLOGY

Pharmacodynamics

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.

The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet ADP receptors, P2Y₁₂, thus inhibiting platelet aggregation. 2-oxoclopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. 2-oxoclopidogrel 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.

Pharmacokinetics

After repeated oral doses of 75 mg per day, a single oral dose of clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

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

The time to peak concentration for Piax was found to be about 45 minutes.

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

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

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

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

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

A bioavailability study was conducted comparing the generic clopidogrel (as hydrogen sulfate) 75mg tablet with the originator clopidogrel (as hydrogen sulfate) 75mg tablet. The generic and originator mean C_{\max} for clopidogrel was 1.55 ng/mL and 1.85 ng/mL, respectively. The C_{\max} point estimate for clopidogrel was 0.94 with the 90% confidence interval between 0.8249 and 1.0698. The generic and originator mean T_{\max} for clopidogrel was 0.89 hr and 0.93hr respectively. The generic and originator mean AUC_{0-t} for clopidogrel was 2.14 ng.hr/mL and 2.30 ng.hr/mL, respectively. The mean AUC_{0-t} point estimate for clopidogrel was 0.92 with the 90% confidence interval between 0.8187 and 1.0408.

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 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: 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.

Race: Pharmacokinetic differences due to race have not been studied.

CLINICAL TRIALS

The safety and efficacy of clopidogrel in preventing vascular ischaemic events has been evaluated in the CAPRIE study, a double-blind clinical trial comparing clopidogrel to aspirin. Three other studies, the CURE, CLARITY and COMMIT studies, compare clopidogrel in combination with aspirin, to placebo with aspirin. These studies are referred to solely for the safety assessment of this medicine.

Myocardial Infarction or Stroke, or Established Peripheral Artery Disease

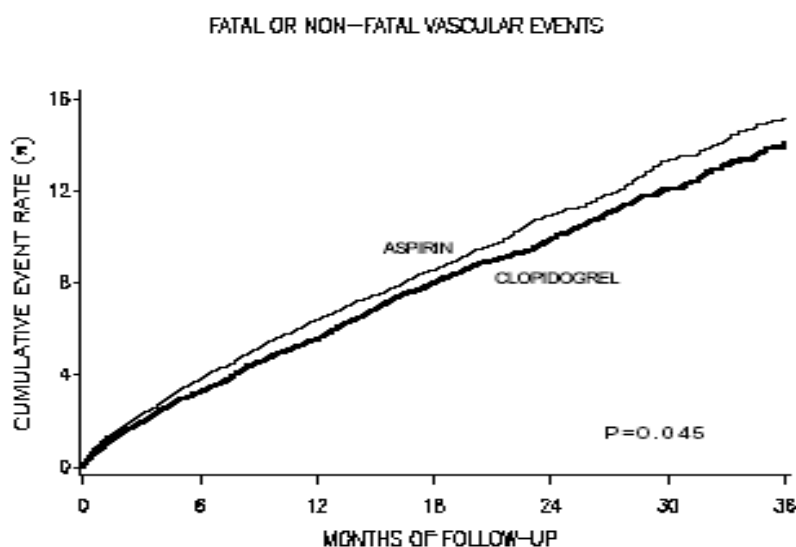
The CAPRIE study included 19,185 patients with established atherosclerosis or history of atherothrombosis as manifested by myocardial infarction, ischaemic stroke or peripheral arterial disease. Patients were randomised to clopidogrel 75 mg/day or aspirin 325 mg/day, and were followed for 1 to 3 years.

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

Patients	Outcome Events of the Primary Analysis	
	Clopidogrel 9599	Aspirin 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% 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 ischemic 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 below. The event curves separated early and continued to diverge over the 3-year follow-up period.



INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to the clopidogrel or any of the excipients.

Severe liver impairment.

Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.

Breast-feeding (see **PRECAUTIONS-Pregnancy and Lactation**).

PRECAUTIONS

General

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

- If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued at least 5 days prior to surgery.
- If the patient is at high risk of ophthalmic bleeding due to intraocular lesions clopidogrel should be used with extra caution.
- Although clopidogrel has shown a lower incidence of gastrointestinal bleeding compared to aspirin in a large controlled clinical trial (CAPRIE), the drug should be used with caution in patients who have lesions with a propensity to bleed. Drugs that might induce such lesions (such as aspirin and Non-Steroidal Anti-Inflammatory Drugs) should be used with caution in patients taking clopidogrel. (see **PRECAUTIONS-Interactions With Other Medicines**).
- 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.

Coronary Artery Bypass Surgery

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

Pharmacogenetics

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

Renal and Hepatic Disorders

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

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

Cardiovascular

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).

Haematological

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment, including plasmapheresis (plasma exchange).

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

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As with other 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.

Carcinogenicity, Mutagenicity and Impairment of Fertility

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

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

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

Use in Pregnancy

Category B1: *Drugs which have been taken by only a limited number of pregnant women and women of child bearing age without an increase in the frequency in the frequency of malformation of other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.*

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 **CONTRAINDICATIONS**).

Interactions with Other Medicines

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 **PRECAUTIONS - General**.

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 gastro-intestinal bleeding and NSAIDs and clopidogrel should be co-administered with caution (See **PRECAUTIONS**).

Glycoprotein IIb/IIIa inhibitors: Clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors.

Thrombolytics: The safety of the concomitant administration of clopidogrel, fibrin or nonfibrin 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 with thrombolytic agents has not been formally established and should be undertaken with caution.

Oral anticoagulants, (including warfarin): The concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleeding.

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 and other drugs which inhibit platelet aggregation may be additive, leading to an increased risk of bleeding.

Other concomitant therapy: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g., omeprazole) should be discouraged.

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

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

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

Drugs metabolised by cytochrome P450 2C9

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

Effects on Ability to Drive and Use Machines

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

ADVERSE 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 four large cardiovascular studies 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.

However, when clopidogrel is used concomitantly with aspirin a small but significant increase in 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) has been observed. 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.

Haematological disorders

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

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

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

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%).

Rash

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

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.

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

BODY SYSTEM/EVENT	CAPRIE	
	% Incidence (% discontinuation)	
	Clopidogrel n = 9599	Aspirin n = 9586
Body as a Whole - general disorders		
Chest pain	8.3 (0.2)	8.3 (0.3)
Accidental/inflicted injury	7.9 (0.1)	7.3 (0.1)
Influenza like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.3 (0.1)	3.4 (0.1)
Cardiovascular disorders - general		
Hypertension	4.3 (<0.1)	5.1* (<0.1)
Central and peripheral nervous system disorders		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
Gastrointestinal		
Abdominal pain	5.6 (0.7)	7.1* (1.0)
Dyspepsia	5.2 (0.6)	6.1* (0.7)
Diarrhoea	4.5* (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)

Adverse events occurring in $\geq 2.5\%$ of patients receiving Clopidogrel in CAPRIE (*continued*)

BODY SYSTEM/EVENT	CAPRIE	
	% Incidence (% discontinuation)	
	Clopidogrel n = 9599	Aspirin n = 9586
Metabolic and nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculoskeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back pain	5.8 (0.1)	5.3 (<0.1)
Myo-, endo-, pericardial and valve disorders		
Angina pectoris	10.1 (0.6)	10.7 (0.4)
Coronary artery disorder	6.2 (0.3)	5.6 (0.3)
Platelet, bleeding and clotting disorders		
Purpura	5.3* (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
Psychiatric disorders		
Depression	3.6 (0.1)	3.9 (0.2)
Resistance mechanism disorders		
Infection	4.7 (<0.1)	4.2 (0.1)
Respiratory system disorders		
Upper respiratory tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnoea	4.5 (0.1)	4.2 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7 (<0.1)
Skin and appendage disorders		
Rash	4.2* (0.5)	3.5 (0.2)
Pruritis	3.3* (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)
Vascular (extracardiac) disorders		
Claudication intermittent	3.8 (0.2)	3.8 (0.2)
Peripheral ischaemia	3.2 (0.2)	3.4 (0.2)
Cerebrovascular disorder	2.6 (0.3)	2.9 (0.3)

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

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

Clinically relevant adverse reactions not listed above pooled from the four major cardiovascular studies, with an incidence of $\geq 0.1\%$, 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*: $\geq 1/1000$ (0.1%) and $< 1/100$ (1%) and *rare*: $\geq 1/10000$ (0.01%) and $< 1/1000$ (0.1%).

Central and peripheral nervous system disorders

- *Uncommon*: Paraesthesia
- *Rare*: Vertigo

Gastrointestinal system disorders

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

Platelet, bleeding and clotting disorders

- *Uncommon*: Bleeding time increased

White cell and RES disorders

- *Uncommon*: Leucopenia and eosinophilia

Post-Marketing Experience

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

Note	<i>very common</i>	$\geq 1/10$ ($\geq 10\%$)
	<i>common</i>	$\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)
	<i>uncommon</i>	$\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1.0\%$)
	<i>rare</i>	$\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)
	<i>very rare</i>	$< 1/10,000$ ($< 0.01\%$)

Musculoskeletal, connective tissue and bone disorders

- *Very rare*: arthralgia, arthritis, myalgia.

Immune system disorders

- *Very rare* : anaphylactoid reactions, serum sickness

Vascular disorders

- *Very rare* : vasculitis, hypotension.

Blood and lymphatic system disorders

- *Uncommon*: eosinophilia, leucopenia, decreased neutrophils, decreased platelets, increased bleeding time
- *Very rare*: serious cases of bleeding, mainly skin, musculoskeletal (haemarthrosis, haematoma), eye (conjunctival, ocular, retinal) and respiratory tract bleeding (haemoptysis, pulmonary haemorrhage),

epistaxis, haematuria and haemorrhage of operative wound. Fatal haemorrhage, including intracranial, gastrointestinal and retroperitoneal haemorrhage.

Cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with aspirin or clopidogrel with aspirin and heparin (see PRECAUTIONS - Interactions with Other Medicines)

- Very rare cases of thrombotic thrombocytopenic purpura (TTP) have been reported
- *Very rare*: aplastic anaemia, neutropenia, pancytopenia, agranulocytosis, granulocytopenia, anaemia

Skin and subcutaneous tissue disorders

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

Psychiatric

- *Very rare*: confusion, hallucinations

Nervous system disorders

- *Very rare*: taste disturbances

Hepatobiliary disorders

- *Very rare*: hepatitis, acute liver failure

Gastrointestinal

- *Very rare*: colitis (including ulcerative or lymphatic colitis), pancreatitis, stomatitis

Respiratory, thoracic and mediastinal disorders

- *Very rare*: bronchospasm, interstitial pneumonitis

Renal and urinary disorders

- *Very rare*: glomerulopathy

Investigations

- *Very rare*: blood creatinine increase, abnormal liver function tests

General disorders and administration site conditions

- *Very rare*: fever, syncope

DOSAGE AND ADMINISTRATION

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

Adults

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

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

Children and Adolescents

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

OVERDOSAGE

Contact the Poisons Information Centre on 131126 (Australia) for advice on the management of 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.

PRESENTATION AND STORAGE CONDITIONS

75 mg tablet – A white, film-coated, round, biconvex, beveled edge tablet debossed with “M” on one side of the tablet and “C27” on the other side.

7*, 14*, 28, 56*, 84*, 112* and 280* tablets packed in blister strips.

4*(sample), 7*, 14*, 28, 50*, 56*, 84*, 112* and 280* tablets packed in bottles*.

* Not marketed in Australia.

Store below 25°C.

POISON SCHEDULE OF THE MEDICINE

S4. Prescription Medicine

NAME AND ADDRESS OF THE SPONSOR

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DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 14 May 2010.

Date of most recent amendment: 30 June 2010.