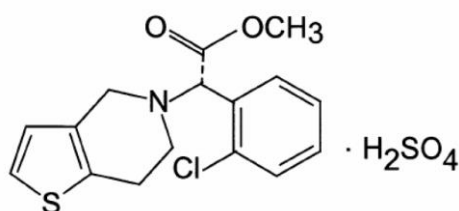

PRODUCT INFORMATION
CLOPIDOGREL SANDOZ 75mg FILM-COATED TABLETS

NAME OF THE MEDICINE

Generic name: Clopidogrel hydrogen sulfate

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



CAS: 120202-66-6 (Clopidogrel hydrogen sulfate)
113 665-84-2 (Clopidogrel base)

Empirical formula: $\text{C}_{16}\text{H}_{16}\text{ClNO}_2\text{S}\cdot\text{H}_2\text{SO}_4$ MW: 419.9

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 $+ 56^\circ$.

Each tablet contains mannitol, microcrystalline cellulose, hydroxypropylcellulose, hydrogenated vegetable oil, Opadry Pink 03B54942 and Opacode S-1-27794 Black.

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 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.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. 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. 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 75mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 7 days after treatment was discontinued.

Pharmacokinetics

After repeated oral doses of 75mg per day, a single oral dose of clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025mg/L) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

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

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

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

Following an oral dose of 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 15mL/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60mL/min) and healthy subjects, after repeated doses of 75mg/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 75mg of clopidogrel per day.

Administration of a single dose of 75mg clopidogrel to healthy subjects under fasting conditions achieved a mean peak plasma concentration of clopidogrel of 605.65pg/mL within 0.76 hours for Clopidogrel Sandoz and 635.81pg/mL within 0.90 hours for a reference clopidogrel film-coated tablet product. The mean AUC_{0-inf} was 978.80pg·h/mL for Clopidogrel Sandoz and 1067.41pg·h/mL for a reference clopidogrel film-coated tablet product. The elimination half-life of clopidogrel was 4.5 hours after single administration of Clopidogrel Sandoz.

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 metabolizers 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 DOSAGE AND ADMINISTRATION).

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 (%) ^{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 TRITONTIMI 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 75mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar in healthy volunteers receiving 75mg of clopidogrel per day. No dosage adjustment is needed in renally impaired patients. However, experience with clopidogrel is limited in patients with severe renal impairment. Therefore clopidogrel should be used with caution in this population.

Gender. No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of 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 PHARMACOLOGY, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

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. In addition, three other studies (CURE, CLARITY and COMMIT) have been conducted for unapproved indications.

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 75mg/day or aspirin 325mg/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.

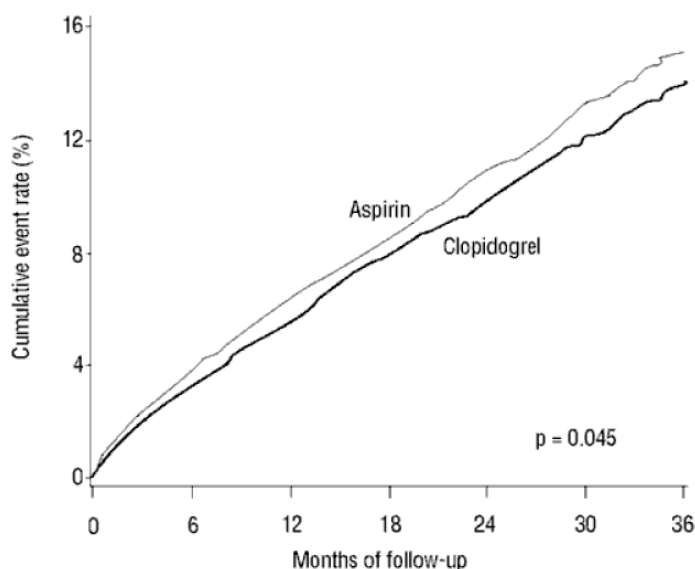
	Outcome Events of the Primary Analysis	
	Clopidogrel	Aspirin
Patients	9599	9586
IS (fatal or not)	438 (4.56%)	461 (4.81%)

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% 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 below. The event curves separated early and continued to diverge over the 3-year follow-up period.

Fatal or non-fatal vascular events



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 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, 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 the drug 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 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 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

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 metabolizers 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 PHARMACOLOGY, Pharmacogenetics and CLINICAL TRIALS, 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 PHARMACOLOGY, 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 DOSAGE AND 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 PHARMACOLOGY, Pharmacogenetics and PRECAUTIONS). 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.

Renal impairment

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

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).

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. 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. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see INTERACTION WITH OTHER MEDICINES).

Acquired haemophilia

Acquired haemophilia has been reported following the 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 ADVERSE 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.

Effects on fertility

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

Use in pregnancy (Category B1)

Clopidogrel and/or its metabolites are known to cross the placenta in pregnant rats and rabbits. However, teratology studies in rats and rabbits at doses up to 500mg and 300mg/kg/day PO, respectively, revealed no evidence of embryotoxicity or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should not be used in women during pregnancy.

Use in lactation

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

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 77mg/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).

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).

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.

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.

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.

Acetylsalicylic acid (ASA). Clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and ASA have been administered together for up to one year.

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 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.

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 PRECAUTIONS).

Selective Serotonin Reuptake Inhibitors (SSRIs). Since SSRI's 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 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.

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. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g. omeprazole) should be discouraged (see PHARMACOLOGY, Pharmacogenetics and PRECAUTIONS). If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantaprazole.

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

Proton Pump Inhibitors (PPI): In a crossover clinical study (N=72 healthy subjects), clopidogrel (300mg loading dose followed by 75mg/day) alone and with omeprazole (80mg at the same time as clopidogrel) were administered for 5 days. Mean maximal platelet aggregation intensity % (MAI) was the primary pharmacodynamics 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 5µM 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 (300mg loading dose followed by 75mg/day) alone and with pantoprazole (80mg at the same time as clopidogrel) for 5 days. Mean maximal platelet aggregation intensity % was the primary pharmacodynamics 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)/pharmacodynamics (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, cimetidine, 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). Co-administration of clopidogrel with warfarin increases the risk of bleeding because independent effects on hemostasis. However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9. It is unlikely that clopidogrel interfered with the metabolism of drugs such as phenytoin and tolbutamide and the NSAID's, 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 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.

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 CAPRIE 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.

Please note the following additional information is sourced from 3 studies that have been conducted for unapproved indications.

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 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

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.

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)

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.

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)
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 CAPRIE, CURE, CLARITY and COMMIT 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: very common $\geq 1/10$ ($\geq 10\%$)

common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)

uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1.0\%$)

rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)

very rare $< 1/10,000$ ($< 0.01\%$)

Musculoskeletal, connective and bone

Very rare: musculo-skeletal bleeding (haemarthrosis), arthralgia, arthritis, myalgia

Immune system disorders

Very rare: anaphylactoid reactions, serum sickness

Unknown: cross-reactive hypersensitivity amongst thienopyridine (such as ticlopidine, prasugrel) (see PRECAUTIONS)

Vascular disorders

Common: haematoma

Very rare: serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension

Blood and lymphatic system disorders

Rare: Neutropenia (including severe neutropenia)

Very rare: serious cases of bleeding, mainly skin, musculo-skeletal (haemarthrosis, haematoma), eye (conjunctival, ocular, retinal) 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 INTERACTIONS WITH OTHER MEDICINES).

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, pancytopenia, agranulocytosis, granulocytopenia, anaemia

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

Skin and Subcutaneous tissue disorders

Common: bruising

Uncommon: rash, pruritus, skin bleeding (purpura)

Very rare: maculopapular, exfoliative or erythematous rash, urticaria, 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 systematic symptoms (DRESS), eczema, lichen planus

Psychiatric

Very rare: confusion, hallucinations

Nervous System disorders

Uncommon: intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness

Very rare: taste disturbances

Eye disorders

Very rare: Serious cases of eye bleeding (conjunctival, ocular, retinal)

Ear and labyrinth disorders

Rare: vertigo

Hepatobiliary disorders

Very rare: hepatitis, acute liver failure, abnormal liver function test

Gastrointestinal disorders

Common: gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia

Uncommon: gastric ulcer and duodenal ulcer, vomiting, gastritis, nausea, constipation, flatulence

Rare: retro-peritoneal haemorrhage

Very rare: gastrointestinal and retroperitoneal haemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

Respiratory, thoracic and mediastinal disorders

Common: Epistaxis

Very rare: respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Renal and Urinary disorders

Uncommon: haematuria

Very rare: glomerulopathy, glomerulonephritis, blood creatinine increased

Investigations

Uncommon: bleeding time prolonged, neutrophil count decreased, platelet count decreased

Very rare: blood creatinine increase, abnormal liver function tests

General disorders and administration site conditions

Common: bleeding at the puncture site

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 75mg.

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

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 PHARMACOLOGY, 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.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of an overdose.

In animals, clopidogrel at single oral doses $\geq 1500\text{mg/kg}$ 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

Clopidogrel Sandoz 75mg film-coated tablets - Pink colored film coated round shaped tablets with $\frac{SZ}{75}$ imprinted on one side and plain on the other side.

Blister pack containing 28 tablets.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 25/11/2009

DATE OF MOST RECENT AMENDMENT: 01/05/2015