CLOPIDOGREL BISULFATE - clopidogrel bisulfate tablet, film coated
REMEDYREPACK INC.

These highlights do not include all the information needed to use clopidogrel tablets safely and effectively. See full prescribing information for clopidogrel tablets. Clopidogrel Tablets, USPInitial U.S. Approval: 1997

Boxed Warning section

The effectiveness of clopidogrel tablets is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1)]*. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel tablets at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy *[see Clinical Pharmacology (12.5)]*. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers *[see Dosage and Administration (2.3)]*.

INDICATIONS & USAGE

Clopidogrel is a $P2Y_{12}$ platelet inhibitor indicated for:

- Acute coronary syndrome
  - For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)] including patients who are to be managed medically and those who are to be managed with coronary revascularization, clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. (1.1)
  - For patients with ST-elevation myocardial infarction (STEMI), 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. The benefit for patients who undergo primary PCI is unknown. (1.1)
- Recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. Clopidogrel has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death. (1.2)

- For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST- elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization, clopidogrel tablets have been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

- For patients with ST-elevation myocardial infarction (STEMI), clopidogrel tablets have been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.

The optimal duration of clopidogrel therapy in ACS is unknown.

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, clopidogrel tablets have been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

DOSAGE & ADMINISTRATION

- Acute coronary syndrome (2.1)
  - Non-ST-segment elevation ACS (UA/NSTEMI): 300 mg loading dose followed by 75 mg once daily, in combination with aspirin (75 mg to 325 mg once daily)
  - STEMI: 75 mg once daily, in combination with aspirin (75 mg to 325 mg once daily), with or

without a loading dose and with or without thrombolytics.
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily (2.2)

Clopidogrel tablets can be administered with or without food *[see Clinical Pharmacology (12.3)]*.

For patients with non-ST-elevation ACS (UA/NSTEMI), initiate clopidogrel tablets with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiate aspirin (75 mg to 325 mg once daily) and continue in combination with clopidogrel tablets *[see Clinical Studies (14.1)]*.

For patients with STEMI, the recommended dose of clopidogrel tablets is 75 mg once daily orally, administered in combination with aspirin (75 mg to 325 mg once daily), with or without thrombolytics. Clopidogrel tablets may be initiated with or without a loading dose *[see Clinical Studies (14.1)]*.

The recommended daily dose of clopidogrel tablets is 75 mg once daily orally, with or without food *[see Clinical Pharmacology (12.3)]*.

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response *[see Clinical Pharmacology (12.5)]*, an appropriate dose regimen for this patient population has not been established.

Avoid using omeprazole or esomeprazole with clopidogrel. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of clopidogrel. When concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite *[see Warnings and Precautions (5.1), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

DOSAGE FORMS & STRENGTHS

- 75 mg tablets: white film-coated, round, unscored tablets debossed with **M** on one side of the tablet and **C27** on the other side.
- 300 mg tablets: white film-coated, oval, unscored tablets debossed with **M C28** on one side of the tablet and blank on the other side.

CONTRAINDICATIONS

- Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)
- Hypersensitivity to clopidogrel or any component of the product (4.2)

Clopidogrel tablets are contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

Clopidogrel tablets are contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product *[see Adverse Reactions (6.2)]*.

WARNINGS AND PRECAUTIONS

- Reduced effectiveness in impaired CYP2C19 function: Avoid concomitant use with omeprazole or esomeprazole. (5.1)
- Bleeding: Clopidogrel increases risk of bleeding. Discontinue 5 days prior to elective surgery. (5.2)
- Discontinuation of clopidogrel: Premature discontinuation increases risk of cardiovascular events. (5.3)
- Recent transient ischemic attack or stroke: Combination use of clopidogrel and aspirin in these patients was not shown to be more effective than clopidogrel alone, but was shown to increase major bleeding. (5.4)
- Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with clopidogrel, including fatal cases. (5.5)

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 *[see Boxed Warning]* and by concomitant medications that interfere with CYP2C19.

Avoid concomitant use of clopidogrel with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel *[see Drug Interactions (7.1) and Dosage and Administration (2.4)]*.

Thienopyridines, including clopidogrel, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue clopidogrel 5 days prior to surgery. In patients who stopped therapy more than 5 days prior to CABG the rates of major bleeding were similar (event rate 4.4% clopidogrel + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within 5 days of CABG, the major bleeding rate was 9.6% for clopidogrel + aspirin, and 6.3% for placebo + aspirin.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7 to 10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.

Avoid lapses in therapy, and if clopidogrel must be temporarily discontinued, restart as soon as possible. Premature discontinuation of clopidogrel may increase the risk of cardiovascular events.

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel has not been shown to be more effective than clopidogrel alone, but the combination has been shown to increase major bleeding.

TTP, sometimes fatal, has been reported following use of clopidogrel, sometimes after a short exposure (< 2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever *[see Adverse Reactions (6.2)]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Bleeding *[see Warnings and Precautions (5.2)]*
- Thrombotic thrombocytopenic purpura *[see Warnings and Precautions (5.5)]*

Because clinical trials are conducted under widely varying conditions and durations of follow up, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clopidogrel has been evaluated for safety in more than 54,000 patients, including over 21,000 patients treated for one year or more. The clinically important adverse reactions observed in trials comparing clopidogrel plus aspirin to placebo plus aspirin and trials comparing clopidogrel alone to aspirin alone are discussed below.

In CURE, clopidogrel use with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (see Table 1). The incidence of intracranial hemorrhage (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise.

The overall incidence of bleeding is described in Table 1.

Table 1: CURE Incidence of Bleeding Complications (% Patients)

Event	Clopidogrel (+ aspirin)* (n = 6,259)	Placebo (+ aspirin)[1] (n = 6,303)
Major Bleeding†	3.7‡	2.7§
Life threatening bleeding	2.2	1.8

Fatal	0.2	0.2
5 g/dL hemoglobin drop	0.9	0.9
Requiring surgical intervention	0.7	0.7
Hemorrhagic strokes	0.1	0.1
Requiring inotropes	0.5	0.5
Requiring transfusion (≥ 4 units)	1.2	1
Other major bleeding	1.6	1
Significantly disabling	0.4	0.3
Intraocular bleeding with significant loss of vision	0.05	0.03
Requiring 2 to 3 units of blood	1.3	0.9
Minor Bleeding¶	5.1	2.4

Ninety-two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.

In COMMIT, similar rates of major bleeding were observed in the clopidogrel and placebo groups, both of which also received aspirin (see Table 2).

Table 2: Incidence of Bleeding Events in COMMIT (% Patients)

Type of bleeding	**Clopidogrel (+ aspirin) (n = 22,961)**	**Placebo (+ aspirin) (n = 22,891)**	**p-value**
Major* noncerebral or cerebral bleeding†	0.6	0.5	0.59
Major noncerebral	0.4	0.3	0.48
Fatal	0.2	0.2	0.90
Hemorrhagic stroke	0.2	0.2	0.91
Fatal	0.2	0.2	0.81
Other noncerebral bleeding (non-major)	3.6	3.1	0.005
Any noncerebral bleeding	3.9	3.4	0.004

In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2% in those taking clopidogrel vs. 2.7% in those taking aspirin; bleeding requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for clopidogrel compared to 0.5% for aspirin.

Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis and hematoma.

In CURE and CHARISMA, which compared clopidogrel plus aspirin to aspirin alone, there was no difference in the rate of adverse events (other than bleeding) between clopidogrel and placebo.

In CAPRIE, which compared clopidogrel to aspirin, pruritus was more frequently reported in those taking clopidogrel. No other difference in the rate of adverse events (other than bleeding) was reported.

The following adverse reactions have been identified during post-approval use of clopidogrel. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and lymphatic system disorders:* Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP)
- *Eye disorders:* Eye (conjunctival, ocular, retinal) bleeding
- *Gastrointestinal disorders:* Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
- *General disorders and administration site condition:* Fever, hemorrhage of operative wound
- *Hepato-biliary disorders:* Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- *Immune system disorders:* Hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Musculoskeletal, connective tissue and bone disorders:* Musculoskeletal bleeding, myalgia, arthralgia, arthritis
- *Nervous system disorders:* Taste disorders, fatal intracranial bleeding, headache
- *Psychiatric disorders:* Confusion, hallucinations
- *Respiratory, thoracic and mediastinal disorders:* Bronchospasm, interstitial pneumonitis, respiratory

tract bleeding
- *Renal and urinary disorders:* Increased creatinine levels
- *Skin and subcutaneous tissue disorders:* Maculopapular or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, erythema multiforme, skin bleeding, lichen planus, generalized pruritus
- *Vascular disorders:* Vasculitis, hypotension

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[1] Other standard therapies were used as appropriate.

[2] Life threatening and other major bleeding.

[3] Major bleeding event rate for clopidogrel + aspirin was dose dependent on aspirin: < 100 mg = 2.6%; 100 mg to 200 mg = 3.5%; > 200 mg = 4.9% Major bleeding event rates for clopidogrel + aspirin by age were: < 65 years = 2.5%, ≥ 65 to < 75 years = 4.1%, ≥ 75 years = 5.9%

[4] Major bleeding event rate for placebo + aspirin was dose dependent on aspirin: < 100 mg = 2%; 100 mg to 200 mg = 2.3%; > 200 mg = 4% Major bleeding event rates for placebo + aspirin by age were: < 65 years = 2.1%, ≥ 65 to < 75 years = 3.1%, ≥ 75 years = 3.6%

[5] Led to interruption of study medication.

[6] Major bleeds were cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

[7] The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for clopidogrel + aspirin by age were: < 60 years = 0.3%, ≥ 60 to < 70 years = 0.7%, ≥ 70 years = 0.8%. Event rates for placebo + aspirin by age were: < 60 years = 0.4%, ≥ 60 to < 70 years = 0.6%, ≥ 70 years = 0.7%.

DRUG INTERACTIONS

- Nonsteroidal anti-inflammatory drugs (NSAIDs): Combination use increases risk of gastrointestinal bleeding. (7.2)
- Warfarin: Combination use increases risk of bleeding. (7.3)

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain 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 *[see Warnings and Precautions (5.1) and Dosage and Administration (2.4)]*.

Avoid concomitant use of clopidogrel with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with clopidogrel. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of clopidogrel than did omeprazole or esomeprazole *[see Dosage and Administration (2.4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Coadministration of clopidogrel and NSAIDs increases the risk of gastrointestinal bleeding.

Although the administration of clopidogrel 75 mg per 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 hemostasis.

However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9.

USE IN SPECIFIC POPULATIONS

Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother. (8.3)

See Section 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the recommended daily human dose, respectively, on a mg/m^2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always

predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Safety and effectiveness in pediatric populations have not been established.

Additional information describing a clinical study in which efficacy was not demonstrated in neonates and infants is approved in the package insert for Bristol-Myers Squibb's clopidogrel tablets. However, due to Bristol-Myers Squibb's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with clopidogrel were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with clopidogrel were 60 years and older, 26% of whom were 70 years and older.

The observed risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Table 1 and Table 2 for the CURE and COMMIT trials, respectively *[see Adverse Reactions (6.1)]*. No dosage adjustment is necessary in elderly patients.

Experience is limited in patients with severe and moderate renal impairment *[see Clinical Pharmacology (12.2)]*.

No dosage adjustment is necessary in patients with hepatic impairment *[see Clinical Pharmacology (12.2)]*.

OVERDOSAGE

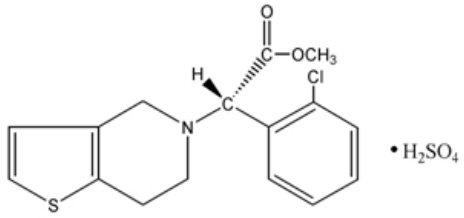
Platelet inhibition by clopidogrel is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.

Based on biological plausibility, platelet transfusion may restore clotting ability.

DESCRIPTION

Clopidogrel bisulfate is a thienopyridine class inhibitor of $P2Y_{12}$ADP platelet receptors. Chemically it is methyl (+)-(*S*)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1). The molecular formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S{\cdot}H_2SO_4$ and its molecular weight is 419.9.

The structural formula is as follows:



Clopidogrel bisulfate, USP is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Clopidogrel tablets, USP for oral administration are provided as either white, round, film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or white, oval, film-coated tablets containing 391.5 mg of clopidogrel bisulfate which is the molar

equivalent of 300 mg of clopidogrel base.

Each tablet contains anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets.

Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet $P2Y_{12}$ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady-state between Day 3 and Day 7. At steady-state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Elderly (≥ 75 years) and young healthy subjects had similar effects on platelet aggregation.

After repeated doses of 75 mg clopidogrel per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.

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

Clopidogrel can be administered with or without food. In a study in healthy male subjects when clopidogrel 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC_{0-24} was unchanged in the presence of food, while there was a 57% decrease in active metabolite C_{max}. Similar results were observed when a clopidogrel 300 mg loading dose was administered with a high fat breakfast.

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. In the 75 mg to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from

dose proportionality: increasing the dose by a factor of four results in 2- and 2.7-fold increases in C_{max} and AUC, respectively.

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-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.

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain inhibitors of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

The effect of proton pump inhibitors (PPI) on the systemic exposure to the clopidogrel active metabolite following multiple doses of clopidogrel 75 mg evaluated in dedicated drug interaction studies is presented in Figure 1.

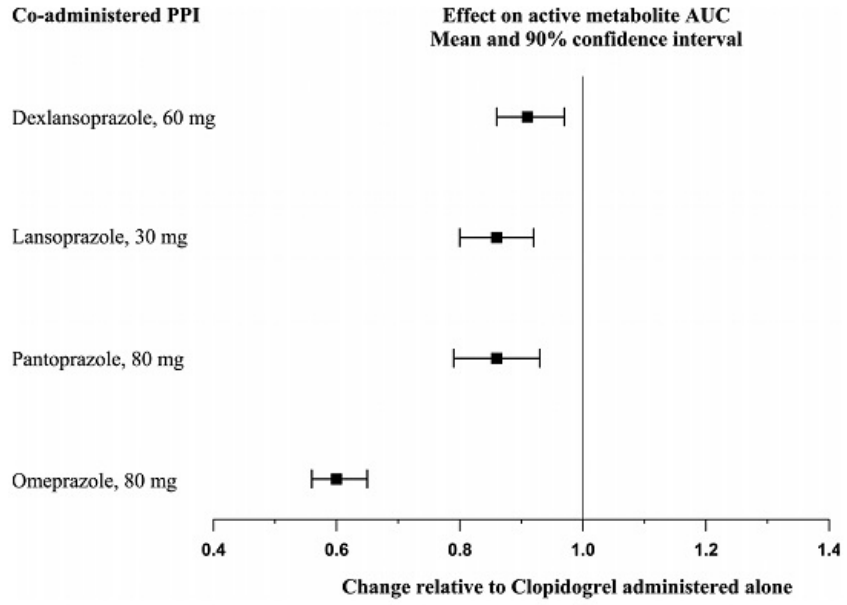


Figure 1: Exposure to Clopidogrel Active Metabolite Following Multiple Doses of Clopidogrel 75 mg Alone or with Proton Pump Inhibitors (PPIs)

Pharmacodynamic and pharmacokinetic parameters measured in these studies showed that the interaction was highest with omeprazole and least with dexlansoprazole.

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. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, ten each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen (see Table 3). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status

	Dose	Ultrarapid (n = 10)	Extensive (n = 10)	Intermediate (n = 10)	Poor (n = 10)
C_{max} (ng/mL)	300 mg (24 h)	24 (10)	32 (21)	23 (11)	11 (4)
	600 mg (24 h)	36 (13)	44 (27)	39 (23)	17 (6)
	75 mg (Day 5)	12 (6)	13 (7)	12 (5)	4 (1)
	150 mg (Day 5)	16 (9)	19 (5)	18 (7)	7 (2)
IPA (%)*	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)
VASP-PRI (%)†	300 mg (24 h)	73 (12)	68 (16)	78 (12)	91 (12)
	600 mg (24 h)	51 (20)	48 (20)	56 (26)	85 (14)
	75 mg (Day 5)	40 (9)	39 (14)	50 (16)	83 (13)
	150 mg (Day 5)	20 (10)	24 (10)	29 (11)	61 (18)

Values are mean (SD)

Some published studies suggest that intermediate metabolizers have decreased active metabolite exposure and diminished antiplatelet effects.

The relationship between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in retrospective analyses of clopidogrel-treated subjects in CHARISMA (n = 2.428) and TRITON-TIMI 38 (n = 1,477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.

[8] Inhibition of platelet aggregation with 5 mcM ADP; larger value indicates greater platelet inhibition

[9] Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition

NONCLINICAL TOXICOLOGY

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures > 25 times that in humans at the recommended daily dose of 75 mg.

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 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 (52 times the recommended human dose on a mg/m^2 basis).

CLINICAL STUDIES

The CURE study included 12,562 patients with ACS without ST-elevation (UA or NSTEMI) and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia. Patients were required to have either ECG changes compatible with new ischemia (without ST-elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. The patient population was largely Caucasian (82%) and included 38% women, and 52% patients ≥ 65 years of age.

Patients were randomized to receive clopidogrel (300 mg loading dose followed by 75 mg once daily) or placebo, and were treated for up to one year. Patients also received aspirin (75 mg to 325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for 3 days prior to randomization.

The number of patients experiencing the primary outcome (CV death, 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% to 28%; $p < 0.001$) for the clopidogrel-treated group (see Table 4).

Table 4: Outcome Events in the CURE Primary Analysis

Outcome	Clopidogrel (+ aspirin)*	Placebo (+ aspirin)[10]	Relative Risk Reduction (%)

	(n = 6,259)	(n = 6,303)	(95% CI)
Primary outcome (Cardiovascular death, MI, stroke)	582 (9.3%)	719 (11.4%)	20% (10.3, 27.9) p < 0.001
All Individual Outcome Events:†			
CV death	318 (5.1%)	345 (5.5%)	7% (-7.7, 20.6)
MI	324 (5.2%)	419 (6.6%)	23% (11, 33.4)
Stroke	75 (1.2%)	87 (1.4%)	14% (-17.7, 36.6)

Most of the benefit of clopidogrel occurred in the first 2 months, but the difference from placebo was maintained throughout the course of the trial (up to 12 months) (see Figure 2).

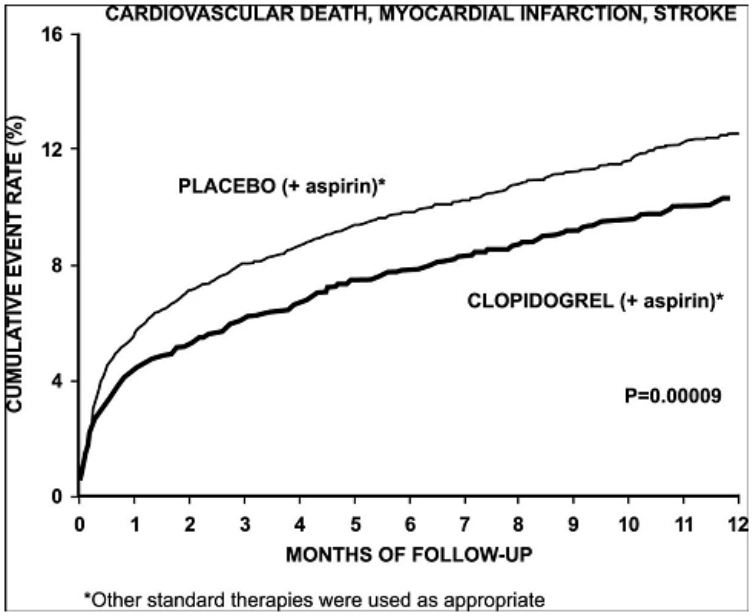


Figure 2: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study

In CURE, the use of clopidogrel was associated with a lower incidence of CV death, MI or stroke in patient populations with different characteristics, as shown in Figure 3. The benefits associated with clopidogrel were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH, intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid-lowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of clopidogrel was observed independently of the dose of aspirin (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study anti-platelet drugs, and chronic NSAIDs was not allowed in CURE.

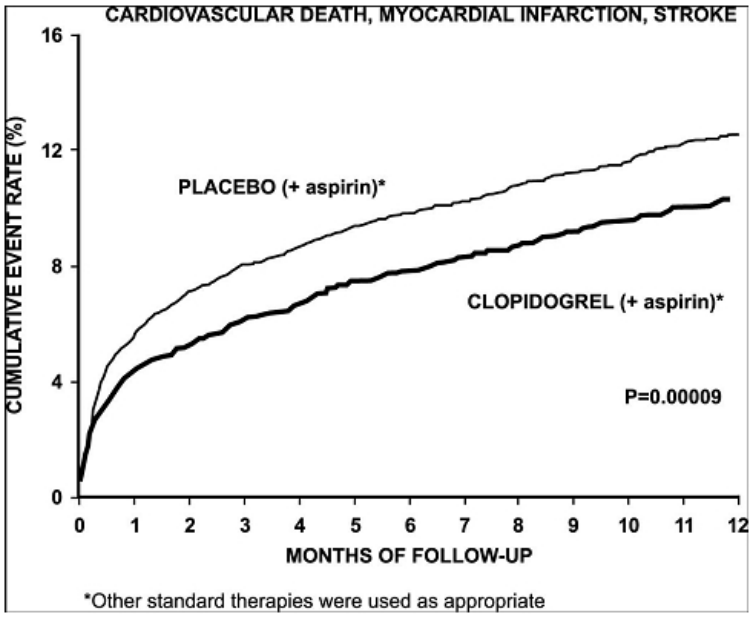


Figure 3: Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study

The use of clopidogrel in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the clopidogrel group, 126 patients [2%] in the placebo group; relative risk reduction of 43%), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the clopidogrel group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%). The use of clopidogrel in CURE did not affect the number of patients treated with CABG or PCI (with or without stenting), (2,253 patients [36%] in the clopidogrel group, 2,324 patients [36.9%] in the placebo group; relative risk reduction of 4%).

In patients with STEMI, the safety and efficacy of clopidogrel were evaluated in the randomized, placebo-controlled, double-blind study, COMMIT. COMMIT included 45,852 patients presenting within 24 hours of the onset of the symptoms of myocardial infarction with supporting ECG abnormalities (i.e., ST-elevation, ST-depression or left bundle-branch block). Patients were randomized to receive clopidogrel (75 mg once daily) or placebo, in combination with aspirin (162 mg per day), for 28 days or until hospital discharge, whichever came first.

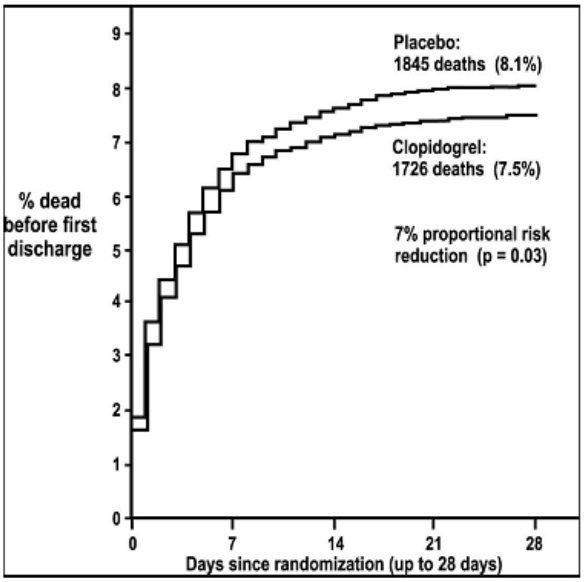
The primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death.

The patient population included 28% women, 58% age ≥ 60 years (26% age ≥ 70 years), 55% patients who received thrombolytics, 68% who received ACE-inhibitors, and only 3% who underwent PCI.

As shown in Table 5 and Figure 4 and Figure 5 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).

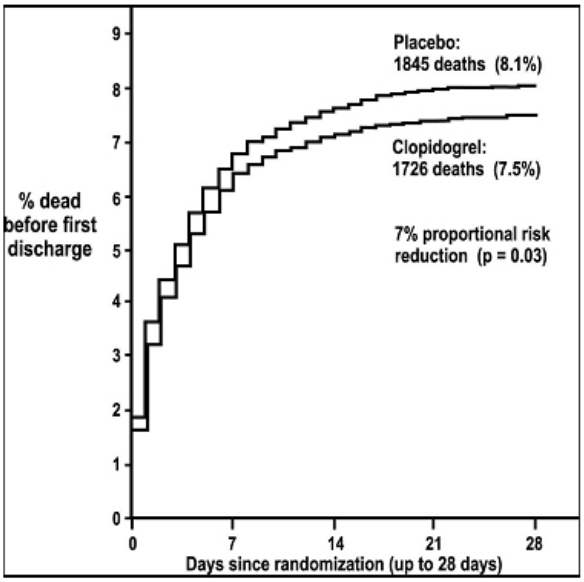
Table 5: Outcome Events in the COMMIT Analysis

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[13]	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.33



* All treated patients received aspirin.

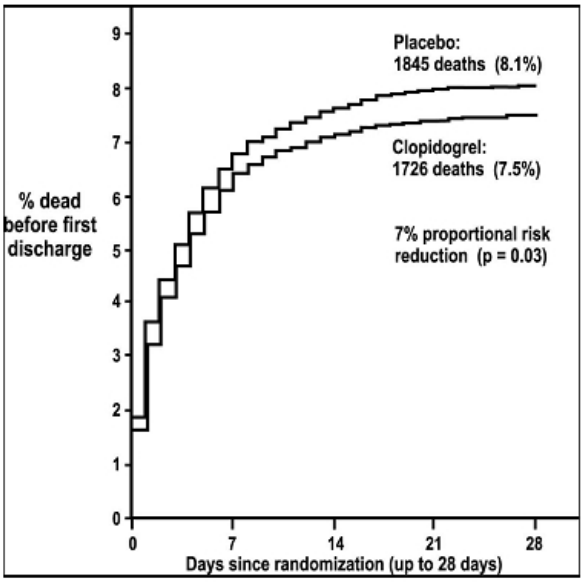
Figure 4: Cumulative Event Rates for Death in the COMMIT Study*



* All treated patients received aspirin.

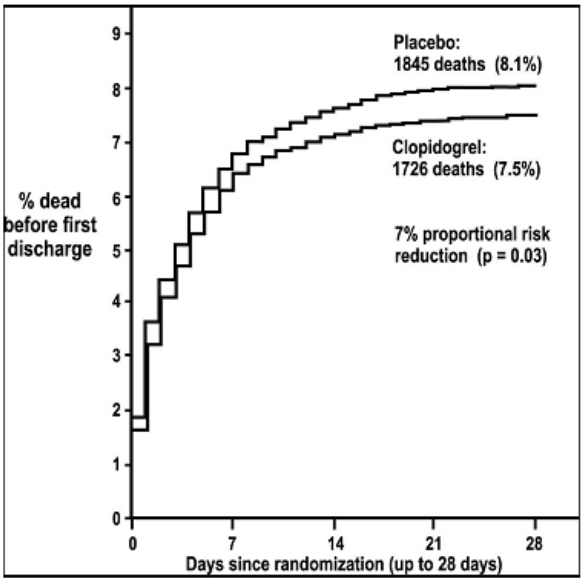
Figure 5: Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study*

The effect of clopidogrel did not differ significantly in various pre-specified subgroups as shown in Figure 6. The effect was also similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history (see Figure 7). Such subgroup analyses should be interpreted cautiously.



* All treated patients received aspirin.

Figure 6: Effects of Adding Clopidogrel to Aspirin on the Combined Primary Endpoint Across Baseline and Concomitant Medication Subgroups for the COMMIT Study



* All treated patients received aspirin.

Figure 7: Effects of Adding Clopidogrel to Aspirin in the Non-Prespecified Subgroups in the COMMIT Study

The CAPRIE trial was a 19,185 patient, 304 center, international, randomized, double-blind, parallel-group study comparing clopidogrel (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or 3) established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 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.

Table 6: Outcome Events in the CAPRIE Primary Analysis

Patients	**Clopidogrel** n = 9,599	**Aspirin** n = 9,586

Ischemic stroke (fatal or not)	438 (4.6%)	461 (4.8%)
MI (fatal or not)	275 (2.9%)	333 (3.5%)
Other vascular death	226 (2.4%)	226 (2.4%)
Total	939 (9.8%)	1,020 (10.6%)

As shown in Table 6, clopidogrel was associated with a lower incidence of outcome events, primarily MI. The overall relative risk reduction (9.8% vs. 10.6%) 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 lower in the clopidogrel group.

The curves showing the overall event rate are shown in Figure 8. The event curves separated early and continued to diverge over the 3-year follow-up period.

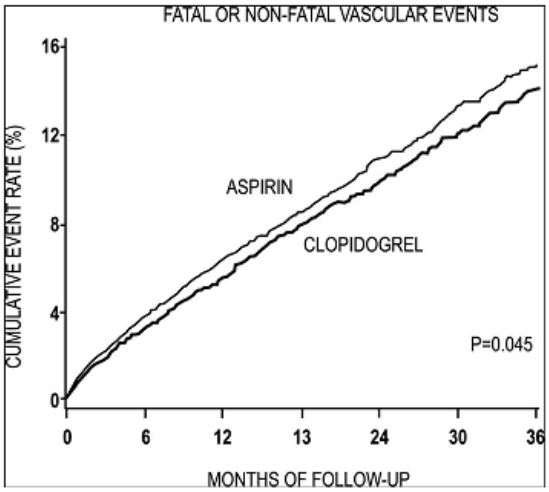


Figure 8: Fatal or Non-Fatal Vascular Events in the CAPRIE Study

The statistical significance favoring clopidogrel over aspirin was marginal (p = 0.045). However, because aspirin is itself effective in reducing cardiovascular events in patients with recent myocardial infarction or stroke, the effect of clopidogrel is substantial.

The CAPRIE trial included a population that was randomized on the basis of three entry criteria. The efficacy of clopidogrel relative to aspirin was heterogeneous across these randomized subgroups (p = 0.043). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of clopidogrel over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was not numerically superior to aspirin.

The CHARISMA trial was a 15,603 subject, randomized, double-blind, parallel group study comparing clopidogrel (75 mg daily) to placebo for prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis. All subjects were treated with aspirin 75 mg to 162 mg daily. The mean duration of treatment was 23 months. The study failed to demonstrate a reduction in the occurrence of the primary endpoint, a composite of CV death, MI, or stroke. A total of 534 (6.9%) patients in the clopidogrel group versus 573 (7.4%) patients in the placebo group experienced a primary outcome event (p = 0.22). Bleeding of all severities was more common in the subjects randomized to clopidogrel.

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[10]Other standard therapies were used as appropriate.

[11]The individual components do not represent a breakdown of the primary and co-primary outcomes, but rather the total number of subjects experiencing an event during the course of the study.

[12]The difference between the composite endpoint and the sum of death + non-fatal MI + non-fatal stroke indicates that nine patients (two clopidogrel and seven placebo) suffered both a non-fatal stroke and a non-fatal MI.

[13]Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

HOW SUPPLIED

Clopidogrel Tablets, USP are available as tablets containing clopidogrel bisulfate, USP equivalent to 75 mg or 300 mg of clopidogrel.

The 75 mg tablet is a white film-coated, round, unscored tablet debossed with **M** on one side of the tablet and **C27** on the other side. They are available as follows:

NDC 0378-3627-93
bottles of 30 tablets

NDC 0378-3627-77
bottles of 90 tablets

NDC 0378-3627-05
bottles of 500 tablets

The 300 mg tablet is a white film-coated, oval, unscored tablet debossed with **M C28** on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-3628-93
bottles of 30 tablets

NDC 0378-3628-77
bottles of 90 tablets

NDC 0378-3628-05
bottles of 500 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

INFORMATION FOR PATIENTS

[See Medication Guide (17.6).]

- Summarize the effectiveness features and potential side effects of clopidogrel.
- Tell patients to take clopidogrel exactly as prescribed.
- Remind patients not to discontinue clopidogrel without first discussing it with the physician who prescribed clopidogrel.

Inform patients that they:
- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

- Inform patients that TTP is a rare but serious condition that has been reported with clopidogrel and other drugs in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

Instruct patients to:
- inform physicians and dentists that they are taking clopidogrel before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping clopidogrel.

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take, including prescription or over-the-counter proton pump inhibitors (e.g., omeprazole), warfarin, or NSAIDs *[see Warnings and Precautions (5)]*.

SPL MEDGUIDE

MEDICATION GUIDE
CLOPIDOGREL TABLETS, USP
(kloe pid′ oh grel)
75 mg and 300 mg

Read this Medication Guide before you start taking clopidogrel tablets and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about clopidogrel tablets?

1. Clopidogrel tablets may not work as well in people who:

- **have certain genetic factors that affect how the body breaks down clopidogrel.** Your doctor may do genetic tests to make sure clopidogrel tablets are right for you.
- **take certain medicines, especially omeprazole (Prilosec®*) or esomeprazole (Nexium®*).** Your doctor may change the medicine you take for stomach acid problems while you take clopidogrel tablets.

2. **Clopidogrel tablets can cause bleeding which can be serious and can sometimes lead to death.** Clopidogrel tablets are a blood thinner medicine that lowers the chance of blood clots forming in your body. While you take clopidogrel tablets:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer for any bleeding to stop

Call your doctor right away if you have any of these signs or symptoms of bleeding:

- unexpected bleeding or bleeding that lasts a long time
- blood in your urine (pink, red or brown urine)
- red or black stools (looks like tar)
- bruises that happen without a known cause or get larger
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds

Do not stop taking clopidogrel tablets without talking to the doctor who prescribes it for you. People who are treated with a stent, and stop taking clopidogrel tablets too soon, have a higher risk of getting a blood clot on the stent, having a heart attack, or dying. If you must stop clopidogrel tablets because of bleeding, your risk of a heart attack may be higher.

What are clopidogrel tablets?

Clopidogrel tablets are a prescription medicine used to treat people who have any of the following:

- chest pain due to heart problems
- poor circulation in their legs (peripheral arterial disease)
- a heart attack
- a stroke

Clopidogrel tablets are used alone or with aspirin to lower your chance of having another serious problem with your heart or blood vessels such as heart attack, stroke, or blood clot that can lead to death.

Platelets are blood cells that help your blood clot normally. Clopidogrel tablets help to prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if clopidogrel tablets are safe and effective in children.

Who should not take clopidogrel tablets?

Do not take clopidogrel tablets if you:

- currently have a condition that causes bleeding, such as a stomach ulcer
- are allergic to clopidogrel or other ingredients in clopidogrel tablets. See the end of this leaflet for a complete list of ingredients in clopidogrel tablets.

What should I tell my doctor before taking clopidogrel tablets?

Before you take clopidogrel tablets, tell your doctor if you:

- have a history of bowel (gastrointestinal) or stomach ulcers
- have a history of bleeding problems
- plan to have surgery or a dental procedure. See "**How should I take clopidogrel tablets?**"
- are pregnant or plan to become pregnant. It is not known if clopidogrel tablets will harm your unborn baby
- are breast-feeding or plan to breast-feed. It is not known if clopidogrel passes into your breast milk. You and your doctor should decide if you will take clopidogrel tablets or breast-feed. You should not do both without talking to your doctor.

Tell all of your doctors and your dentist that you are taking clopidogrel tablets. They should talk to the doctor who prescribed clopidogrel tablets for you before you have any surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription, non-prescription medicines, vitamins and herbal supplements.

Clopidogrel tablets may affect the way other medicines work, and other medicines may affect how

clopidogrel tablets work. See "**What is the most important information I should know about clopidogrel tablets?**"

Taking clopidogrel tablets with certain other medicines may increase your risk of bleeding.

Especially tell your doctor if you take:

- aspirin, especially if you have had a stroke. Always talk to your doctor about whether you should take aspirin along with clopidogrel tablets to treat your condition.
- Non-steroidal anti-inflammatory drugs (NSAIDs). Ask your doctor or pharmacist for a list of NSAID medicines if you are not sure.
- warfarin (Coumadin®*, Jantoven®*)

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take clopidogrel tablets?

- Take clopidogrel tablets exactly as your doctor tells you.
- Do not change your dose or stop taking clopidogrel tablets without talking to your doctor first. Stopping clopidogrel tablets may increase your risk of heart attack or stroke.
- Take clopidogrel tablets with aspirin as instructed by your doctor.
- You can take clopidogrel tablets with or without food.
- If you miss a dose, take clopidogrel tablets as soon as you remember. If it is almost time for your next dose, skip the missed dose. Take the next dose at your regular time. Do not take two doses of clopidogrel tablets at the same time unless your doctor tells you to.
- If you take too much clopidogrel tablets, call your doctor or go to the nearest emergency room right away.
- Talk with your doctor about stopping your clopidogrel tablets before you have surgery. Your doctor may tell you to stop taking clopidogrel tablets at least 5 days before you have surgery to avoid excessive bleeding during surgery.

What are the possible side effects of clopidogrel tablets?

Clopidogrel tablets can cause serious side effects including:

- See "**What is the most important information I should know about clopidogrel tablets?**"
- **A blood clotting problem called Thrombotic Thrombocytopenic Purpura (TTP).** TTP can happen with clopidogrel tablets, sometimes after a short time (less than 2 weeks). TTP is a blood clotting problem where blood clots form in blood vessels; and can happen anywhere in the body. TTP needs to be treated in a hospital right away, because it may cause death. Get medical help right away if you have any of these symptoms and they can not be explained by another medical condition:

- purplish spots (called purpura) on the skin or in the mouth (mucous membranes) due to bleeding under the skin
- your skin or the whites of your eyes are yellow (jaundice)
- you feel tired or weak
- your skin looks very pale
- fever
- fast heart rate or feeling short of breath
- headache
- speech changes
- confusion
- coma
- stroke
- seizure
- low amount of urine, or urine that is pink or has blood in it
- stomach area (abdominal) pain
- nausea, vomiting, or diarrhea
- vision changes

Tell your doctor if you have any side effect that bothers you or that does not go

away.

These are not all the possible side effects of clopidogrel tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store clopidogrel tablets?

- Store clopidogrel tablets at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Keep clopidogrel tablets and all medicines out of the reach of children.

General information about clopidogrel tablets

Medicines are sometimes used for purposes other than those listed in a Medication Guide. Do not take clopidogrel tablets for a condition for which it was not prescribed. Do not give clopidogrel tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about clopidogrel tablets. If you would like more information, talk to your doctor. Ask your doctor or pharmacist for information about clopidogrel tablets that was written for healthcare professionals.

For more information, call 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients in clopidogrel tablets?

Active ingredient: clopidogrel bisulfate

Inactive ingredients: anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate and titanium dioxide

This Medication Guide has been approved by the U.S. Food and Drug Administration.

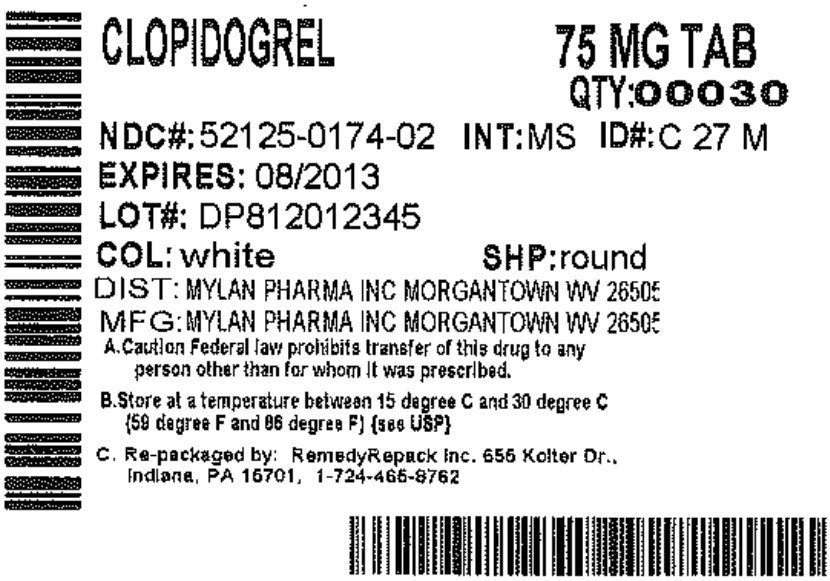
*The brands listed are trademarks of their respective owners.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

MARCH 2012
CLOP:R1mmt

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION

DRUG: Clopidogrel Bisulfate
GENERIC: clopidogrel
DOSAGE: TABLET, FILM COATED
ADMINSTRATION: ORAL
NDC: 52125-174-02
STRENGTH:75 mg
COLOR: white
SHAPE: ROUND
SCORE: No score
SIZE: 9 mm
IMPRINT: 30
QTY: 30



CLOPIDOGREL BISULFATE

clopidogrel tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:52125-174(NDC:0378-3627)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CLOPIDOGREL BISULFATE (CLOPIDOGREL)	CLOPIDOGREL	75 mg

Inactive Ingredients	
Ingredient Name	**Strength**

ANHYDROUS LACTOSE	
COLLOIDAL SILICON DIOXIDE	
CROSCARMELLOSE SODIUM	
HYPROMELLOSES	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYDEXTROSE	
POLYETHYLENE GLYCOLS	
SODIUM LAURYL SULFATE	
TITANIUM DIOXIDE	

Product Characteristics

Color	white	**Score**	no score
Shape	ROUND (TABLET, FILM COATED)	**Size**	9mm
Flavor		**Imprint Code**	M;C27
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52125-174-02	30 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077665	03/26/2013	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 3/2013 REMEDYREPACK INC.