

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CLOPIDOGREL Tablets, USP safely and effectively. See full prescribing information for CLOPIDOGREL Tablets, USP.

**CLOPIDOGREL Tablets, USP for Oral Use**  
Initial U.S. Approval: 1997

<b>WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS</b> <i>See full prescribing information for complete boxed warning.</i>
<ul style="list-style-type: none"><li>Effectiveness of Clopidogrel tablets depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)</li> <li>Patients treated with Clopidogrel tablets at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)</li> <li>Tests are available to identify a patient’s CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)</li> <li>Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)</li></ul>
<b>INDICATIONS AND USAGE</b>
Clopidogrel is a P2Y <sub>12</sub> platelet inhibitor indicated for:
<ul style="list-style-type: none"><li>Acute coronary syndrome <ul style="list-style-type: none"><li>For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], 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)</li> <li>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)</li></ul></li> <li>Recent MI, recent stroke, or established peripheral arterial disease. Clopidogrel has been shown to reduce the combined endpoint of new ischemic stroke, new MI, and other vascular death. (1.2)</li></ul>

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<b>DOSAGE AND ADMINISTRATION</b>
<ul style="list-style-type: none"><li>Acute coronary syndrome (2.1) <ul style="list-style-type: none"><li>UA/NSTEMI: 300 mg loading dose followed by 75 mg once daily, in combination with aspirin (75 to 325 mg once daily)</li> <li>STEMI: 75 mg once daily, in combination with aspirin (75 to 325 mg once daily), with or without a loading dose</li></ul></li> <li>Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily (2.2)</li></ul>
<b>DOSAGE FORMS AND STRENGTHS</b>
Tablets: 75 mg, 300 mg (3)
<b>CONTRAINDICATIONS</b>
<ul style="list-style-type: none"><li>Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)</li> <li>Hypersensitivity to Clopidogrel or any component of the product (4.2)</li></ul>
<b>WARNINGS AND PRECAUTIONS</b>
<ul style="list-style-type: none"><li>CYP2C19 inhibitors: Avoid concomitant use of omeprazole or esomeprazole. (5.1)</li> <li>Bleeding: Clopidogrel increases risk of bleeding. Discontinue 5 days prior to elective surgery. (5.2)</li> <li>Premature discontinuation increases risk of cardiovascular events. (5.3)</li> <li>Recent transient ischemic attack or stroke: Combination use of Clopidogrel and aspirin is not more effective than clopidogrel alone, but increases major bleeding. (5.4)</li> <li>Thrombotic thrombocytopenic purpura (TTP) has been reported. (5.5)</li> <li>Cross-reactivity among thienopyridines has been reported. (5.6)</li></ul>
<b>ADVERSE REACTIONS</b>
Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 866-695-1995 or FDA at 1-800-FDA-1088 or <a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a> .
<b>DRUG INTERACTIONS</b>
<ul style="list-style-type: none"><li>Nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs, SNRIs): Increases risk of bleeding. (7.2, 7.3, 7.4)</li></ul>
<b>USE IN SPECIFIC POPULATIONS</b>
Nursing mothers: Discontinue drug or nursing. (8.3)
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## DESCRIPTION

<b>Major bleeding †</b>	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	1.0
Other major bleeding	1.6	1.0
Significantly disabling	0.4	0.3
Intraocular bleeding with significant loss of vision	0.05	0.03
Requiring 2-3 units of blood	1.3	0.9
Minor bleeding ¶	5.1	2.4

† Other standard therapies were used as appropriate.
‡ Life-threatening and other major bleeding.
§ 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 = 5.3%
§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg = 2.0%; 100 mg to 200 mg = 2.3%; >200 mg = 4.0%
Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years = 3.6%
¶ Led to interruption of study medication.

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.

<b>Event</b>	<b>Clopidogrel (+ aspirin)* (n=6259)</b>	<b>Placebo (+ aspirin)* (n=6303)</b>
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‡ 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 <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%.
¶ CAPRI (Clopidogrel vs. Aspirin)

In CAPRI, gastrointestinal hemorrhage occurred at a rate of 2.0% 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 hematomas.

**Other Adverse Events**
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 CAPRI, 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.

### 6.2 Postmarketing Experience

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), acquired hemophilia A
- 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, eosinophilic pneumonia
- Renal and urinary disorders:** Increased creatinine levels
- Skin and subcutaneous tissue disorders:** Maculopapular, erythematous or exfoliative rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, skin bleeding, lichen planus, generalized pruritus
- Vascular disorders:** Vasculitis, hypotension

## 7 DRUG INTERACTIONS

### 7.1 CYP2C19 Inhibitors

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)]*.

#### *Proton Pump Inhibitors (PPI)*

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)]*.

#### **7.2 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

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

#### **7.3 Warfarin (CYP2C9 Substrates)**

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.

#### **7.4 SSRIs and SNRIs**

Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

#### **8 USE IN SPECIFIC POPULATIONS**

##### 8.1 Pregnancy

#### *Pregnancy Category B*

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<sup>2</sup> 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.

#### **8.3 Nursing Mothers**

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 reaction 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.

#### **8.4 Pediatric Use**

Safety and effectiveness in pediatric populations have not been established.

A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

#### **8.5 Geriatric Use**

Of the total number of subjects in the CAPRI 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 Reactors (6.1)]*. No dosage adjustment is necessary in elderly patients.

#### **8.6 Renal Impairment**

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

#### **8.7 Hepatic Impairment**

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

#### **10 OVERDOSAGE**

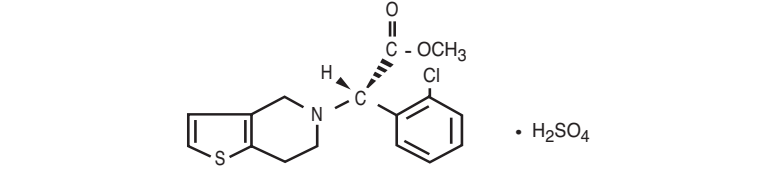
Platelet inhibition by clopidogrel is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms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

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

#### **11 DESCRIPTION**

Clopidogrel bisulfate is a thienopyridine class inhibitor of P2Y<sub>12</sub> ADP platelet receptors. Chemically it is methyl (+)-(-)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is C<sub>16</sub>H<sub>16</sub>ClNO<sub>2</sub>S<sup>+</sup>·H<sub>2</sub>SO<sub>4</sub> 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 freely soluble in methanol, practically insoluble in ether. It has a specific optical rotation of about +56°.

Clopidogrel tablets, USP for oral administration is provided as either pink colored, round shaped, biconvex, de-bossed, film coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or pink colored, modified oval shaped, de-bossed film coated tablets containing 391.5 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.

Each tablet contains microcrystalline cellulose, mannitol, croscarmellose sodium, hydroxy propyl cellulose, hydroxy propyl methyl cellulose and hydrogenated castor oil as inactive ingredients. The film coating contains hypromellose, titanium dioxide, polyethylene glycol and red iron oxide.

#### **12.1 CLINICAL PHARMACOLOGY**

##### **12.1 Mechanism of Action**

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y<sub>12</sub> class of ADP receptors on platelets.

##### **12.2 Pharmacodynamics**

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<sub>12</sub> 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.

#### *Geriatric Patients*

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

#### *Renally-Impaired Patients*

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.

#### *Hepatically-Impaired Patients*

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.

#### *Gender*

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

#### **12.3 Pharmacokinetics**

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

#### *Absorption*

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.

#### *Effect of Food*

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<sub>0-24</sub> was unchanged in the presence of food, while there was a 57% decrease in active metabolite C<sub>max</sub>. Similar results were observed when a clopidogrel 300 mg loading dose was administered with a high-fat breakfast.

#### *Metabolism*

Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

The C<sub>max</sub> 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<sub>max</sub> occurs approximately 30 to 60 minutes after dosing. In the 75 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 2.0- and 2.7-fold increases in C<sub>max</sub> and AUC, respectively.

#### *Elimination*

Following an oral dose of <sup>14</sup>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 metabol



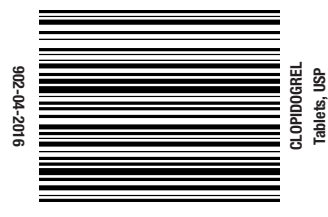


Figure 3: Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study

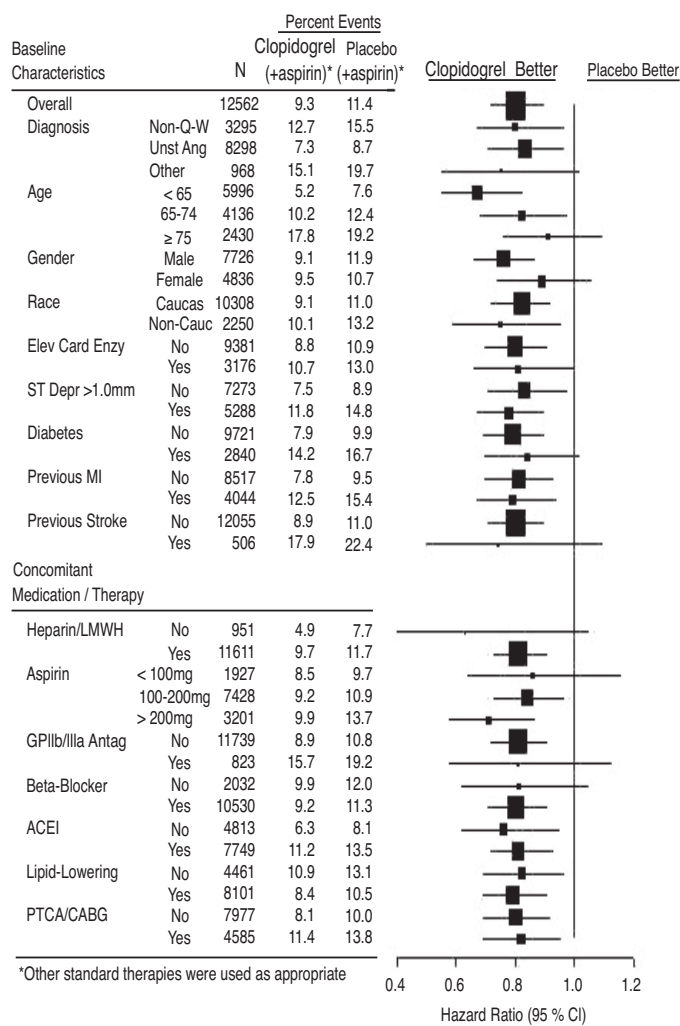
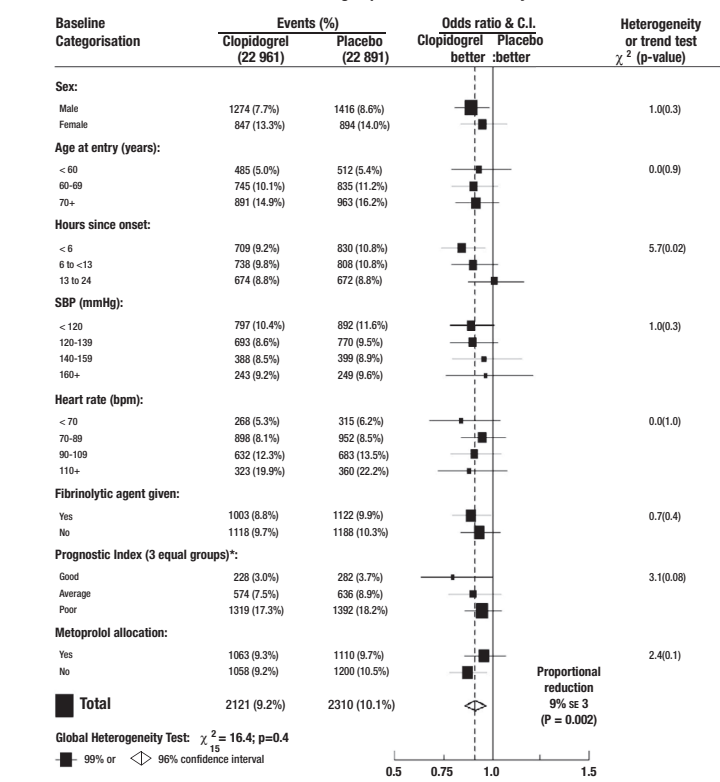
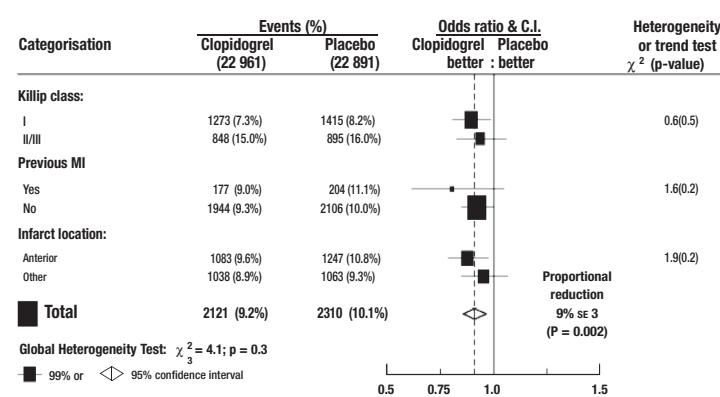


Figure 6: Effects of Adding Clopidogrel to Aspirin on the Combined Primary Endpoint across Baseline and Concomitant Medication Subgroups for the COMMIT Study



\* Three similar-sized prognostic index groups were based on absolute risk of primary composite outcome for each patient calculated from baseline prognostic variables (excluding allocated treatments) with a Cox regression model.

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



14.2 Recent Myocardial Infarction, Recent Stroke, or Established Peripheral Arterial Disease

CAPRIE

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.

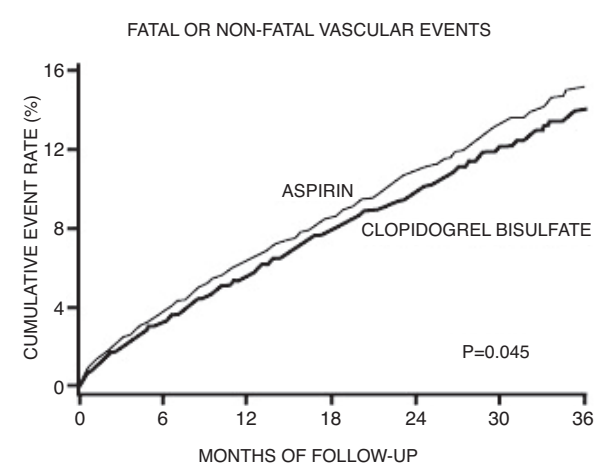
Table 6: Outcome Events in the CAPRIE Primary Analysis

Table with 3 columns: Patients, Clopidogrel (n=9,599), Aspirin (n=9,586). Rows include Ischemic stroke (fatal or not), MI (fatal or not), Other vascular death, Total.

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 6.7%, 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 3 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.

14.3 Lack of Established Benefit of Clopidogrel plus Aspirin in Patients with Multiple Risk Factors or Established Vascular Disease

CHARISMA

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 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.

16 HOW SUPPLIED/STORAGE AND HANDLING Clopidogrel tablets, USP 75 mg are available as pink colored, round shaped, biconvex, film coated tablets de-bossed on one side with SG and 124 on other side. They are available as follows:

- NDC 31722-901-30: Bottles of 30 tablets
NDC 31722-901-90: Bottles of 90 tablets
NDC 31722-901-01: Bottles of 100 tablets
NDC 31722-901-05: Bottles of 500 tablets
NDC 31722-901-10: Bottles of 1000 tablets

Clopidogrel tablets, USP 300 mg are available as pink colored, modified oval shaped, film coated tablets de-bossed on one side with SG and 121 on other side. They are available as follows:

- NDC 31722-902-30: Bottles of 30 tablets
NDC 31722-902-90: Bottles of 90 tablets
NDC 31722-902-01: Bottles of 100 tablets
NDC 31722-902-05: Bottles of 500 tablets

Store at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

PHARMACIST: Dispense a Medication Guide with each prescription.

17 PATIENT COUNSELING INFORMATION

[See Medication Guide]

17.1 Benefits and Risks

- 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.

17.2 Bleeding

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.

17.3 Other Signs and Symptoms Requiring Medical Attention

- 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.

17.4 Invasive Procedures

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.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take [see Warnings and Precautions (5) and Drug Interactions (7)]. Coumadin® is a registered trademark of Bristol-Myers Squibb Pharma Company. Prilosec® and Nexium® are registered trademark of AstraZeneca. Jantoven® is a registered trademark of USL Pharma.

Manufactured for: Camber Pharmaceuticals, Inc. Piscataway, NJ 08854

Manufactured by: ScieGen Pharmaceuticals, Inc. Hauppauge, NY 11788 USA

Revised: April 2016

MEDICATION GUIDE CLOPIDOGREL (kloe pid' oh grel) TABLETS, USP 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?

- Clopidogrel tablets may not work as well in people who:
have certain genetic factors that affect how the body breaks down clopidogrel.
take certain medicines, especially omeprazole (Prilosec®) or esomeprazole (Nexium®).
Clopidogrel tablets can cause bleeding which can be serious and can sometimes lead to death.

2. Clopidogrel tablets can cause bleeding which can be serious and can sometimes lead to death.

- 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 stop taking clopidogrel tablets too soon have a higher risk of 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.
are pregnant or plan to become pregnant.
are breastfeeding or plan to breastfeed.
have had an allergy or reaction to any medicine used to treat your disease.

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 works. 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®)
selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Ask your doctor or pharmacist for a list of SSRI or SNRI medicines if you are not sure.

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.
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.
Talk with your doctor about stopping your clopidogrel tablets before you have 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).
purplish spots (called purpura) on the skin or in the mouth
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. Tell your doctor if you develop an allergic reaction including skin reactions while taking clopidogrel tablets.

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, USP?

- Store clopidogrel tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

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.

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, contact Hetero Labs Limited at 866-495-1995.

What are the ingredients in clopidogrel tablets?

Active ingredient: clopidogrel bisulfate, USP

Inactive ingredients:

Tablet: microcrystalline cellulose, mannitol, croscarmellose sodium, hydroxy propyl cellulose, hydroxy propyl methyl cellulose and hydrogenated castor oil

Film coating: Hypromellose, titanium dioxide, polyethylene glycol and red iron oxide. This Medication Guide has been approved by the U.S. Food and Drug Administration.

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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 [2.0%] 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), (2253 patients [36.0%] in the clopidogrel group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.0%).

COMMIT 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).

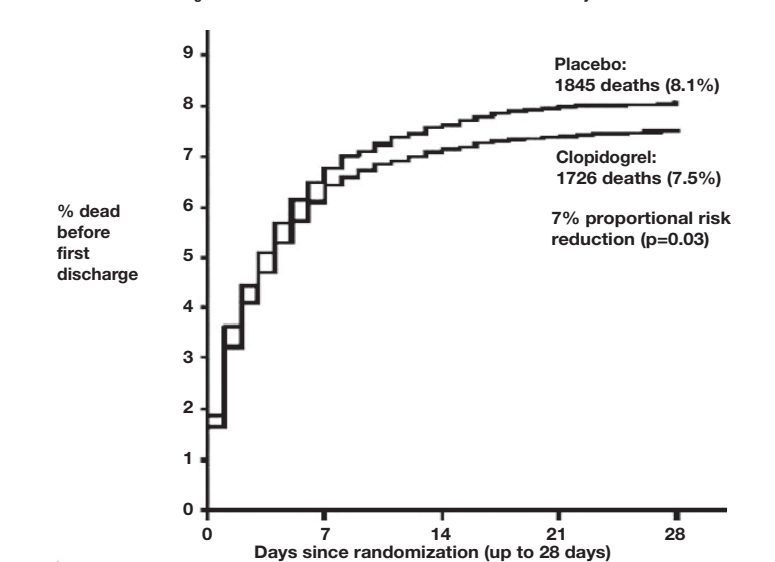
Table 5: Outcome Events in the COMMIT Analysis

Table with 5 columns: Event, Clopidogrel (+ aspirin) (N=22,961), Placebo (+ aspirin) (N=22,891), Odds ratio (95% CI), p-value. Rows include Composite endpoint: Death, MI, or Stroke\*, Death, Non-fatal MI\*\*, Non-fatal Stroke\*\*.

\* The difference between the composite endpoint and the sum of death+non-fatal MI+non-fatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a non-fatal stroke and a non-fatal MI.

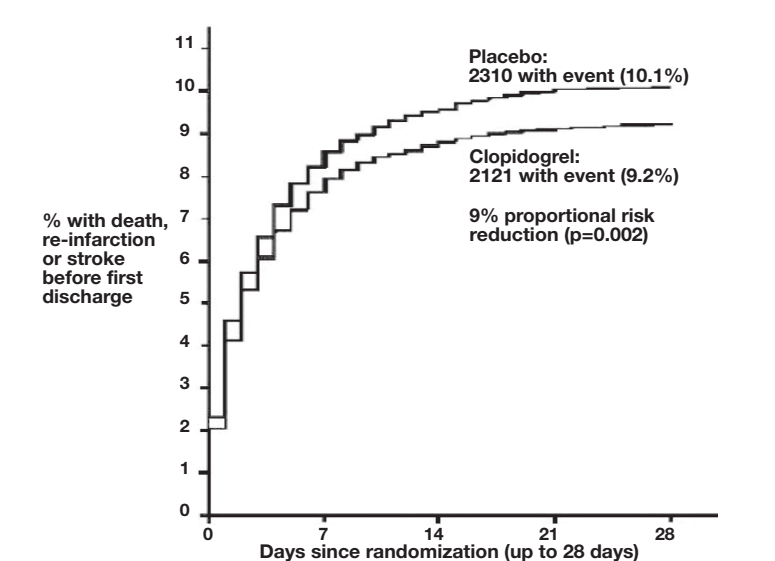
\*\* Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

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\*



\* All treated patients received aspirin.

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.