CLOPIDOGREL BISULFATE - clopidogrel bisulfate  tablet, film coated
Apopex Corp.

DESCRIPTION
Clopidogrel bisulfate is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GP IIb/IIIa complex. Chemically it is methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is C₁₆H₁₆ClNO₂S•H₂SO₄ and its molecular weight is 419.9.

The structural formula is as follows:

Clopidogrel bisulfate 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 75 mg for oral administration are provided as reddish-brown, round, unscored, film coated tablets, imprinted "APO" on one side and "CL" over "75" on the other side. The tablets contain 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base.

Each tablet contains anhydrous lactose, colloidal silicon dioxide, crospovidone, methylcellulose and zinc stearate as inactive ingredients. The reddish-brown film coating contains ferric oxide, hydroxypropyl cellulose, hypromellose 2910 15 CPS, polyethylene glycol 8000 and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action
Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbidity events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

Pharmacodynamic Properties
Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GP IIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel bisulfate. Repeated doses of 75 mg clopidogrel bisulfate 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 bisulfate 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.

Pharmacokinetics and Metabolism
After repeated 75 mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma.

Following an oral dose of ¹⁴C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of Food
Administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.
Absorption and Distribution
Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable in vitro up to a concentration of 100 µg/mL.

Metabolism and Elimination
In vitro and in vivo, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Populations

Geriatric Patients
Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients
After repeated doses of 75 mg clopidogrel bisulfate per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of clopidogrel bisulfate per day.

Gender
No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race
Pharmacokinetic differences due to race have not been studied.

CLINICAL STUDIES
The clinical evidence for the efficacy of clopidogrel bisulfate is derived from two double-blind trials: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of clopidogrel bisulfate to aspirin, and the CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), a comparison of clopidogrel bisulfate to placebo, both given in combination with aspirin and other standard therapy.

The CAPRIE trial was a 19,185 patient, 304 center, international, randomized, double-blind, parallel-group study comparing clopidogrel bisulfate (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) objectively 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 1: Outcome Events in the CAPRIE Primary Analysis

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel bisulfate</th>
<th>aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>9599</td>
<td>9586</td>
</tr>
<tr>
<td>IS (fatal or not)</td>
<td>438 (4.6%)</td>
<td>461 (4.8%)</td>
</tr>
<tr>
<td>MI (fatal or not)</td>
<td>275 (2.9%)</td>
<td>333 (3.5%)</td>
</tr>
<tr>
<td>Other vascular death</td>
<td>226 (2.4%)</td>
<td>226 (2.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>939 (9.8%)</td>
<td>1020 (10.6%)</td>
</tr>
</tbody>
</table>

As shown in the table, clopidogrel bisulfate was associated with a lower incidence of outcome events of every kind. The overall 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 again lower in the clopidogrel bisulfate group.

The curves showing the overall event rate are shown in Figure 1. The event curves separated early and continued to diverge over the 3-year follow-up period.

**Figure 1: Fatal or Non-Fatal Vascular Events in the CAPRIE Study**

![Figure 1: Fatal or Non-Fatal Vascular Events in the CAPRIE Study](image)

Although the statistical significance favoring clopidogrel bisulfate over aspirin was marginal (P=0.045), and represents the result of a single trial that has not been replicated, the comparator drug, aspirin, is itself effective (vs. placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus, the difference between clopidogrel bisulfate and placebo, although not measured directly, is substantial.

The CAPRIE trial included a population that was randomized on the basis of 3 entry criteria. The efficacy of clopidogrel bisulfate 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 bisulfate 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 bisulfate was not numerically superior to aspirin.

In the meta-analyses of studies of aspirin vs. placebo in patients similar to those in CAPRIE, aspirin was associated with a reduced incidence of atherothrombotic events. There was a suggestion of heterogeneity in these studies too, with the effect strongest in patients with a history of myocardial infarction, weaker in patients with a history of stroke, and not discernible in patients with a history of peripheral vascular disease. With respect to the inferred comparison of clopidogrel bisulfate to placebo, there is no indication of heterogeneity.

The CURE study included 12,562 patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave myocardial infarction) 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 segment 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 bisulfate (300 mg loading dose followed by 75 mg/day) or placebo, and were treated for up to one year. Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization.

The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 (9.30%) in the clopidogrel bisulfate-treated group and 719 (11.41%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%–28%; p=0.00009) for the clopidogrel bisulfate-treated group (see Table 2).

At the end of 12 months, the number of patients experiencing the co-primary outcome (CV death, MI, stroke or refractory ischemia) was 1035 (16.54%) in the clopidogrel bisulfate-treated group and 1187 (18.83%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%–21%, p=0.00005) for the clopidogrel bisulfate-treated group (see Table 2).

In the clopidogrel bisulfate-treated group, each component of the two primary endpoints (CV death, MI, stroke, refractory ischemia) occurred less frequently than in the placebo-treated group.

**Table 2: Outcome Events in the CURE Primary Analysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel bisulfate (+ aspirin)*</th>
<th>Placebo (+ aspirin)*</th>
<th>Relative Risk Reduction (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=6259)</td>
<td>(n=6303)</td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>582 (9.3%)</td>
<td>719 (11.4%)</td>
<td>20% (10.3, 27.9) p=0.00009</td>
</tr>
<tr>
<td>(Cardiovascular death, MI, Stroke)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-primary outcome</td>
<td>1035 (16.5%)</td>
<td>1187 (18.8%)</td>
<td>14% (6.2, 20.6) p=0.00052</td>
</tr>
<tr>
<td>(Cardiovascular death, MI, Stroke, Refractory Ischemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Individual Outcome Events:†</td>
<td>318 (5.1%)</td>
<td>345 (5.5%)</td>
<td>7% (-7.7, 20.6)</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>CV death</td>
<td>318 (5.1%)</td>
<td>345 (5.5%)</td>
<td>7% (-7.7, 20.6)</td>
</tr>
<tr>
<td>MI</td>
<td>324 (5.2%)</td>
<td>419 (6.6%)</td>
<td>23% (11.0, 33.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>75 (1.2%)</td>
<td>87 (1.4%)</td>
<td>14% (-17.7, 36.6)</td>
</tr>
<tr>
<td>Refractory ischemia</td>
<td>544 (8.7%)</td>
<td>587 (9.3%)</td>
<td>7% (-4.0, 18)</td>
</tr>
</tbody>
</table>

*Other standard therapies were used as appropriate.
†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.

The benefits of clopidogrel bisulfate were maintained throughout the course of the trial (up to 12 months).

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

In CURE, the use of clopidogrel bisulfate 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 tablets were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH (low molecular weight heparin), IV glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid-lowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of clopidogrel bisulfate was observed independently of the dose of aspirin (75–325 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**

![Figure 3](image-url)
The use of clopidogrel bisulfate in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the clopidogrel bisulfate group, 126 patients [2%] in the placebo group; relative risk reduction of 43%, P=0.0001), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the clopidogrel bisulfate group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%, P=0.003). The use of clopidogrel bisulfate in CURE did not impact the number of patients treated with CABG or PCI (with or without stenting), (2253 patients [36%] in the clopidogrel bisulfate group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4%, P=0.1658).

**INDICATIONS AND USAGE**

Clopidogrel bisulfate is indicated for the reduction of atherothrombotic events as follows:

- **Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
  For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, clopidogrel bisulfate has 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.

- **Acute Coronary Syndrome**
  For patients with acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, clopidogrel bisulfate...
has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

CONTRAINDICATIONS
The use of clopidogrel bisulfate is contraindicated in the following conditions:
• Hypersensitivity to the drug substance or any component of the product.
• Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS

Thrombotic thrombocytopenic purpura (TTP)
TTP has been reported rarely following use of clopidogrel bisulfate, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and 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.)

PRECAUTIONS

General
Clopidogrel bisulfate prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel bisulfate should be discontinued 5 days prior to surgery. Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see ADVERSE REACTIONS).

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

GI Bleeding
In CAPRIE, clopidogrel bisulfate was associated with a rate of gastrointestinal bleeding of 2%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs 0.7% (clopidogrel bisulfate + aspirin vs. placebo + aspirin, respectively). Clopidogrel bisulfate should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking clopidogrel bisulfate.

Use in Hepatically Impaired Patients
Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel bisulfate should be used with caution in this population.

Use in Renally Impaired Patients
Experience is limited in patients with severe renal impairment. Clopidogrel bisulfate should be used with caution in this population.

Information for Patients
Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they take clopidogrel bisulfate or clopidogrel bisulfate combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking clopidogrel bisulfate and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

Drug Interactions
Study of specific drug interactions yielded the following results:

Aspirin
Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by clopidogrel bisulfate. Clopidogrel bisulfate potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel bisulfate and aspirin have been administered together for up to one year.

Heparin
In a study in healthy volunteers, clopidogrel bisulfate did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by clopidogrel bisulfate.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
In healthy volunteers receiving naproxen, concomitant administration of clopidogrel bisulfate was associated with increased occult gastrointestinal blood loss. NSAIDs and clopidogrel bisulfate should be coadministered with caution.

Warfarin
Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel bisulfate should be undertaken with caution. (See PRECAUTIONS–General.)

Other Concomitant Therapy
No clinically significant pharmacodynamic interactions were observed when clopidogrel bisulfate was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel bisulfate was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the coadministration of clopidogrel bisulfate.

At high concentrations in vitro, clopidogrel inhibits \( \text{P}_{450} \) (2C9). Accordingly, clopidogrel bisulfate may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with clopidogrel bisulfate.

In addition to the above specific interaction studies, patients entered into clinical trials with clopidogrel bisulfate received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy, heparins (unfractionated and LMWH) and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions. The use of oral anticoagulants, non-study anti-platelet drug and chronic NSAIDs was not allowed in CURE and there are no data on their concomitant use with clopidogrel.

Drug/Laboratory Test Interactions
None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility
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).

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 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 bisulfate should be used during pregnancy only if clearly needed.

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 reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established.

Geriatric Use
Of the total number of subjects in controlled clinical studies, approximately 50% of patients treated with clopidogrel bisulfate were 65 years of age and over. Approximately 16% of patients treated with clopidogrel bisulfate were 75 years of age and over. The observed difference in risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figure 3 (see CLINICAL STUDIES). The observed difference in risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Table 3 (see ADVERSE REACTIONS).
ADVERSE REACTIONS

Clopidogrel bisulfate has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1 year or more. The overall tolerability of clopidogrel bisulfate in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE and CURE are discussed below.

Hemorrhagic: In CAPRIE patients receiving clopidogrel bisulfate, gastrointestinal hemorrhage occurred at a rate of 2%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for clopidogrel bisulfate compared to 0.5% for aspirin.

In CURE, clopidogrel bisulfate use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 3). There was an excess in major bleeding in patients receiving clopidogrel bisulfate plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidences of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups.

The overall incidence of bleeding is described in Table 3 for patients receiving both clopidogrel and aspirin in CURE.

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel bisulfate (+ aspirin)</th>
<th>Placebo (+ aspirin)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3.7 ±</td>
<td>2.7 $</td>
<td>0.001</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>2.2</td>
<td>1.8</td>
<td>0.13</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>5 g/dL hemoglobin drop</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Requiring surgical intervention</td>
<td>0.7</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic strokes</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Requiring inotropes</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Requiring transfusion (≥4 units)</td>
<td>1.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>1.6</td>
<td>1</td>
<td>0.005</td>
</tr>
<tr>
<td>Significantly disabling</td>
<td>0.4</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Intraocular bleeding with significant loss of vision</td>
<td>0.05</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Requiring 2–3 units of blood</td>
<td>1.3</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5.1</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Other standard therapies were used as appropriate.
†Life threatening and other major bleeding.
‡Major bleeding event rate for clopidogrel bisulfate + aspirin was dose-dependent on aspirin: <100 mg=2.6%; 100–200 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%
¶Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg=2%; 100–200 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%
¶Led to interruption of study medication.

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

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% clopidogrel bisulfate + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel bisulfate + aspirin, and 6.3% for placebo + aspirin.

Neutropenia/agranulocytosis: Ticlopidine, a drug chemically similar to clopidogrel bisulfate, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/µL). In CAPRIE severe neutropenia was observed in six patients, four on clopidogrel bisulfate and two on aspirin. Two of the 9599 patients who received clopidogrel bisulfate and none of the 9586 patients who received aspirin had neutrophil counts of zero. One of the four clopidogrel bisulfate patients in CAPRIE was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with clopidogrel bisulfate. In CURE, the numbers of patients with thrombocytopenia (19 clopidogrel bisulfate + aspirin vs. 24 placebo + aspirin) or neutropenia (3 vs. 3) were similar.

Although the risk of myelotoxicity with clopidogrel bisulfate thus appears to be quite low, this possibility should be considered when a patient receiving clopidogrel bisulfate demonstrates fever or other sign of infection.
Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel bisulfate was 27.1%, compared to 29.8% in those receiving aspirin in the CAPRIE trial. In the CURE trial the incidence of these gastrointestinal events for patients receiving clopidogrel bisulfate + aspirin was 11.7% compared to 12.5% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of peptic, gastric or duodenal ulcers was 0.7% for clopidogrel bisulfate and 1.2% for aspirin. In the CURE trial the incidence of peptic, gastric or duodenal ulcers was 0.4% for clopidogrel bisulfate + aspirin and 0.3% for placebo + aspirin.

Cases of diarrhea were reported in the CAPRIE trial in 4.5% of patients in the clopidogrel bisulfate group compared to 3.4% in the aspirin group. However, these were rarely severe (clopidogrel bisulfate=0.2% and aspirin=0.1%). In the CURE trial, the incidence of diarrhea for patients receiving clopidogrel bisulfate + aspirin was 2.1% compared to 2.2% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for clopidogrel bisulfate and 4% for aspirin. In the CURE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for clopidogrel bisulfate + aspirin compared with 0.8% for placebo + aspirin.

Rash and Other Skin Disorders: In the CAPRIE trial, the incidence of skin and appendage disorders in patients receiving clopidogrel bisulfate was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious). In the CURE trial the incidence of rash or other skin disorders in patients receiving clopidogrel bisulfate + aspirin was 4% compared to 3.5% for those receiving placebo + aspirin.

In the CAPRIE trial, the overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for clopidogrel bisulfate and 0.8% for aspirin. In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for clopidogrel bisulfate + aspirin compared with 0.3% for placebo + aspirin.

Adverse events occurring in ≥2.5% of patients on clopidogrel bisulfate in the CAPRIE controlled clinical trial are shown below regardless of relationship to clopidogrel bisulfate. The median duration of therapy was 20 months, with a maximum of 3 years.

<table>
<thead>
<tr>
<th>Body System</th>
<th>% Incidence (% Discontinuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel bisulfate</td>
</tr>
<tr>
<td></td>
<td>[n=9599]</td>
</tr>
<tr>
<td>Body as a Whole general disorders</td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td>8.3 (0.2)</td>
</tr>
<tr>
<td>Accidental/Inflicted injury</td>
<td>7.9 (0.1)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>7.5 (&lt;0.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>6.4 (0.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.3 (0.1)</td>
</tr>
<tr>
<td>Cardiovascular disorders, general</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>4.1 (&lt;0.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.3 (&lt;0.1)</td>
</tr>
<tr>
<td>Central &amp; peripheral nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7.6 (0.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6.2 (0.2)</td>
</tr>
<tr>
<td>Gastrointestinal system disorders</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.6 (0.7)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5.2 (0.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.5 (0.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.4 (0.5)</td>
</tr>
<tr>
<td>Metabolic &amp; nutritional disorders</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4.0 (0)</td>
</tr>
<tr>
<td>Musculo-skeletal system disorders</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6.3 (0.1)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>5.8 (0.1)</td>
</tr>
<tr>
<td>Platelet, bleeding, &amp; clotting disorders</td>
<td></td>
</tr>
<tr>
<td>Purpura/Bruse</td>
<td>5.3 (0.3)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2.9 (0.2)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Clopidogrel bisulfate</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td></td>
<td>[n=6259]</td>
</tr>
<tr>
<td>% Incidence (% Discontinuation)</td>
<td></td>
</tr>
<tr>
<td><strong>Body System</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Upper resp tract infection</td>
<td>8.7 (&lt;0.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4.5 (0.1)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4.2 (0.1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.7 (0.1)</td>
</tr>
<tr>
<td>Coughing</td>
<td>3.1 (&lt;0.1)</td>
</tr>
<tr>
<td><strong>Skin &amp; appendage disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4.2 (0.5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.3 (0.3)</td>
</tr>
<tr>
<td><strong>Urinary system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.1 (0)</td>
</tr>
</tbody>
</table>

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

Adverse events occurring in $\geq 2.0\%$ of patients on clopidogrel bisulfate in the CURE controlled clinical trial are shown below regardless of relationship to clopidogrel bisulfate.

Table 5: Adverse Events Occurring in $\geq 2.0\%$ of Clopidogrel Bisulfate Patients in CURE

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel bisulfate (+ aspirin)*</th>
<th>Placebo (+ aspirin)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole– general disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2.7 (&lt;0.1)</td>
<td>2.8 (0.0)</td>
</tr>
<tr>
<td>Central &amp; peripheral nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3.1 (0.1)</td>
<td>3.2 (0.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.4 (0.1)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Gastrointestinal system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.3 (0.3)</td>
<td>2.8 (0.3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2 (0.1)</td>
<td>1.9 (&lt;0.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.1 (0.1)</td>
<td>2.2 (0.1)</td>
</tr>
</tbody>
</table>

*Other standard therapies were used as appropriate.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving clopidogrel bisulfate in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to clopidogrel bisulfate. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).


Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received clopidogrel bisulfate in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to clopidogrel bisulfate. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

Postmarketing Experience
The following events have been reported spontaneously from worldwide postmarketing experience:

- **Body as a whole:**
  - hypersensitivity reactions, anaphylactoid reactions, serum sickness

- **Central and Peripheral Nervous System disorders:**
  - confusion, hallucinations, taste disorders

- **Hepato-biliary system disorders:**
  - abnormal liver function test, hepatitis (non-infectious), acute liver failure

- **Platelet, Bleeding and Clotting disorders:**
  - cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
  - thrombotic thrombocytopenic purpura (TTP) – some cases with fatal outcome- (see WARNINGS).
  - agranulocytosis, aplastic anemia/pancytopenia
  - conjunctival, ocular and retinal bleeding

- **Respiratory, thoracic and mediastinal disorders:**
  - bronchospasm, interstitial pneumonitis

- **Skin and subcutaneous tissue disorders:**
  - angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus

- **Renal and urinary disorders:**
  - glomerulopathy, increased creatinine levels

- **Vascular disorders:**
  - vasculitis, hypotension

- **Gastrointestinal disorders:**
  - colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

- **Musculoskeletal, connective tissue and bone disorders:**
  - myalgia

OVERDOSAGE
Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent 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 (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment
Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of clopidogrel bisulfate if quick reversal is required.

DOSAGE AND ADMINISTRATION

**Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
The recommended daily dose of clopidogrel tablets is 75 mg once daily.

**Acute Coronary Syndrome**
For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), clopidogrel bisulfate should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with clopidogrel bisulfate. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see CLINICAL STUDIES).

Clopidogrel tablets can be administered with or without food.
No dosage adjustment is necessary for elderly patients or patients with renal disease (See Clinical Pharmacology: Special Populations.)
HOW SUPPLIED
Clopidogrel Tablets USP, 75 mg are reddish-brown, round, unscored, film coated tablets, imprinted "APO" on one side and "CL" over "75" on the other side. They are supplied as follows:
Bottles of 30            NDC 60505-0253-1
Bottles of 90            NDC 60505-0253-2
Bottles of 1000         NDC 60505-0253-3
100 Unit Dose           NDC 60505-0253-4

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

APOTEX INC.
CLOPIDOGREL TABLETS USP, 75 mg
Manufactured by:        Manufactured for:
Apotex Inc.        Apotex Corp.
Toronto, Ontario    Weston, Florida
Canada M9L 1T9     USA 33326
August 2006
Rev. 12