CLOPIVAS Tablets (Clopidogrel bisulfate)

**Black Box Warning: Diminished Effectiveness In Poor Metabolizers**

The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. 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 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. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

**Composition**

CLOPIVAS 75
Each film-coated tablet contains:
Clopidogrel (as bisulfate) ...... 75 mg

CLOPIVAS 300
Each film-coated tablet contains:
Clopidogrel (as bisulfate) ...... 300 mg

**Dosage Form**

Tablet

**Pharmacology**

**Mechanism of Action**

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y₁₂ class of adenosine diphosphate (ADP) receptors on platelets.

**Inhibition of Platelet Aggregation**

Clopidogrel must be metabolized by cytochrome P450 (CYP450) enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of ADP to its platelet P2Y₁₂ receptor and the subsequent ADP-mediated activation of the glycoprotein (GP) IIb/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.

### 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 area under curve (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.

**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 CYP450 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 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_{max} and AUC, respectively.

**Excretion**
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.
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, 10 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 (Table 1). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Table 1: Active metabolite pharmacokinetics and antiplatelet responses by CYP2C19 metabolizer status

<table>
<thead>
<tr>
<th>Dose</th>
<th>Ultrapid (n=10)</th>
<th>Extensive (n=10)</th>
<th>Intermediate (n=10)</th>
<th>Poor (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg (24 h)</td>
<td>24 (10)</td>
<td>32 (21)</td>
<td>23 (11)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
<td>36 (13)</td>
<td>44 (27)</td>
<td>39 (23)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
<td>12 (6)</td>
<td>13 (7)</td>
<td>12 (5)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
<td>16 (9)</td>
<td>19 (5)</td>
<td>18 (7)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>IPA (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg (24 h)</td>
<td>40 (21)</td>
<td>39 (28)</td>
<td>37 (21)</td>
<td>24 (26)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
<td>51 (28)</td>
<td>49 (23)</td>
<td>56 (22)</td>
<td>32 (25)</td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
<td>56 (13)</td>
<td>58 (19)</td>
<td>60 (18)</td>
<td>37 (23)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
<td>68 (18)</td>
<td>73 (9)</td>
<td>74 (14)</td>
<td>61 (14)</td>
</tr>
<tr>
<td><strong>VASP-PRI (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg (24 h)</td>
<td>73 (12)</td>
<td>68 (16)</td>
<td>77 (12)</td>
<td>91 (12)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
<td>51 (20)</td>
<td>48 (20)</td>
<td>56 (26)</td>
<td>85 (14)</td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
<td>40 (9)</td>
<td>39 (14)</td>
<td>50 (16)</td>
<td>83 (13)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
<td>20 (10)</td>
<td>24 (10)</td>
<td>29 (11)</td>
<td>61 (18)</td>
</tr>
</tbody>
</table>

Values are mean (SD)

*Inhibition of platelet aggregation with 5 mcM ADP; larger value indicates greater platelet inhibition
†Vasodilation-stimulated phosphoprotein—platelet reactivity index; smaller value indicates greater platelet inhibition

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 or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.

### Indications

#### Acute Coronary Syndrome

For patients with non-ST-segment elevation acute coronary syndrome (ACS), 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, 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 MI (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 percutaneous coronary intervention (PCI) is unknown. The optimal duration of clopidogrel therapy in ACS is unknown.

#### Recent MI, Recent Stroke or Established Peripheral Arterial Disease

For patients with a history of recent MI, recent stroke, or established peripheral arterial disease (PAD), clopidogrel 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 deaths.

### Dosage And Administration

#### Acute Coronary Syndrome

CLOPIVAS can be administered with or without food. For patients with non-ST-elevation ACS (UA/NSTEMI), initiate with a single oral loading dose of CLOPIVAS 300 and then continue at CLOPIVAS 75 once daily. Initiate aspirin (75 to 325 mg once daily) and continue in combination with CLOPIVAS.

For patients with STEMI, the recommended dose is CLOPIVAS 75 once daily orally, administered in combination with aspirin (75 to 325 mg once daily), with or without thrombolytics. CLOPIVAS may be initiated with or without a loading dose.

#### Recent MI, Recent Stroke or Established PAD

The recommended dose is CLOPIVAS 75 once daily orally, with or without food.

#### CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response, an appropriate dose regimen for this patient population has not been established.
Use with Proton-Pump Inhibitors

Avoid using omeprazole or esomeprazole with CLOPIVAS. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of clopidogrel. When concomitant administration of a proton-pump inhibitor (PPI) is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.

Contraindications

Active pathological bleeding such as peptic ulcer or intracranial hemorrhage
Hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product

Warnings And Precautions

Drug Interactions

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.

Proton Pump Inhibitors: Avoid concomitant use of CLOPIVAS 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.

Nonsteroidal Anti-Inflammatory Drugs: Coadministration of clopidogrel and nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of gastrointestinal bleeding.

Glycoprotein IIb/IIIa Inhibitors: Clopidogrel should be used with caution in patients who receive concomitant GP IIb/IIIa inhibitors.

Acetylsalicylic Acid: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of aspirin twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and aspirin have been administered together for up to one year.

Heparin: In a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Oral Anticoagulants: The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleeding. Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or international normalized ratio (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.
Thrombolytics: The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute MI. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with aspirin.

Selective Serotonin-Reuptake Inhibitors and Serotonin Norepinephrine-Reuptake Inhibitors: 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.

Other Medicinal Products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen. The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption. Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel. Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GP IIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

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 and by concomitant medications that interfere with CYP2C19.

Proton Pump Inhibitors

Avoid concomitant use of CLOPIVAS with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel.

General Risk of Bleeding

Thienopyridines, including clopidogrel, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue CLOPIVAS five days prior to surgery. In patients who stopped therapy more than five days prior to coronary artery bypass graft (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 five 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 (7-10 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.

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with aspirin), and that they should report any unusual bleeding (site or duration) to their physician.

Discontinuation of Clopidogrel

Avoid lapses in therapy, and if CLOPIVAS must be temporarily discontinued, restart as soon as possible. Premature discontinuation of CLOPIVAS may increase the risk of cardiovascular events.
Patients with Recent Transient Ischemic Attack or Stroke

In patients with recent transient ischemic attack (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.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (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 seen on peripheral smear}, neurological findings, renal dysfunction, and fever.

Acquired Hemophilia

Acquired hemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated partial thromboplastin time (aPTT) prolongation with or without bleeding, acquired hemophilia should be considered. Patients with a confirmed diagnosis of acquired hemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Cross-Reactivity among Thienopyridines

Hypersensitivity, including rash, angioedema or hematologic reaction, has been reported in patients receiving clopidogrel, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines.

Renal Impairment

Experience is limited in patients with severe and moderate renal impairment.

Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment.

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/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies with clopidogrel in pregnant women. Because animal reproduction studies are not always predictive of a human response, CLOPIVAS should be used during pregnancy only if clearly needed.

Lactation

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether clopidogrel 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 CLOPIVAS, taking into account the importance of the drug to the mother.

Pediatric Use

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

A randomized, placebo-controlled trial (CLAIRINET) 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.

Geriatric Use

Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with clopidogrel were aged 65 years and older, and 15% were aged 75 years and older. In COMMIT, approximately 58% of the patients treated with clopidogrel were aged 60 years and older, 26% of whom were aged 70 years and older. No dosage adjustment is necessary in elderly patients.

Undesirable Effects

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

Bleeding

TTP

Clinical Studies Experience

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 1 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.

Bleeding

In the CURE trial, use of clopidogrel with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (Table 2). 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.

Table 2: Incidence of bleeding complications (% patients) in the CURE trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel (+ aspirin)* (n=6,259)</th>
<th>Placebo (+ aspirin)* (n=6,303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding&quot;&quot;&quot;&quot;</td>
<td>3.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>5 g/dL hemoglobin drop</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Requiring surgical intervention</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Hemorrhagic strokes</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Requiring inotropes</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Requiring transfusion (&gt;4 units)</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>
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 to 3 units of blood | 1.3 | 0.9
Minor bleeding\(^6\) | 5.1 | 2.4

\(^*\) Other standard therapies were used as appropriate.
\(^**/\^\) Life-threatening and other major bleeding.

\(^6\) Major bleeding event rate for clopidogrel + aspirin was dose-dependent on aspirin: <100 mg = 2.6%; 100 to 200 mg = 3.5%; >200 mg = 4.9%

Major bleeding event rates for clopidogrel + aspirin by age were: <65 years = 2.5%, \(\geq\) 65 to <75 years = 4.1%, \(\geq\) 75 years = 5.9%

\(^\d\) Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg = 2.0%; 100 to 200 mg = 2.3%; >200 mg = 4.0%

Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, \(\geq\) 65 to <75 years = 3.1%, \(\geq\) 75 years = 3.6%

\(^\d\) 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.

In the COMMIT trial, similar rates of major bleeding were observed in the clopidogrel and placebo groups, both of which also received aspirin (Table 3).

Table 3: Incidence of bleeding events in COMMIT (% patients)

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

\(^*\) Major bleeds were cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

\(^**/\^\) 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%, \(\geq\) 60 to <70 years = 0.7%, \(\geq\) 70 years = 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, \(\geq\) 60 to <70 years = 0.6%, \(\geq\) 70 years = 0.7%.
In the CAPRIE trial comparing clopidogrel with aspirin, 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 hematoma.

**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 the CAPRIE trial that 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.

Some adverse events that were reported include – thrombocytopenia, leucopenia, neutropenia (including severe neutropenia), granulocytopenia, anemia, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel), paresthesia, dizziness, vertigo, abdominal pain, dyspepsia, gastritis, vomiting, nausea, constipation, flatulence, gynecomastia, glomerulonephritis, hematuria.

**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, 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 Conditions**: 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 or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, 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

**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 1,500 or 2,000 mg/kg was lethal to mice and to rats and at 3,000 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.
**Incompatibility**

Not applicable

**Shelf-Life**

CLOPIVAS 75: 1 year  
CLOPIVAS 300: 2 years

**Storage And Handling Instructions**

Store in a cool, dry place. Protect from moisture.

**Packaging Information**

CLOPIVAS 75: Strip of 15 tablets  
CLOPIVAS 300: Strip of 2 tablets  
Last Updated: Feb 2016  
Last Reviewed: Feb 2016

CLOPIVAS Tablets

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