CLOPIVAS-AP Tablets (Clopidogrel + Aspirin)

Composition

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

CLOPIVAS-AP 150
Each film-coated tablet contains:
Clopidogrel (as bisulfate) ...... 75 mg
and Aspirin USP ............ 150 mg

Dosage Form

Tablets

Description

CLOPIVAS-AP is a fixed-dose combination containing clopidogrel and aspirin.

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. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP.

Aspirin is also an antiplatelet agent, which acts by causing irreversible inhibition of the cyclooxygenase enzyme. This leads to decreased formation of thromboxane A2.

Pharmacology

Pharmacodynamics

Clopidogrel
**Mechanism of Action**
Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y\(_{12}\) class of ADP receptors on platelets.

**Inhibition of Platelet Aggregation**
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 ADP to its platelet P2Y\(_{12}\) 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.

**Aspirin**
Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and the production of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

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**Pharmacokinetics**

**Clopidogrel**
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.

**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 $C_{\text{max}}$ 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. $C_{\text{max}}$ 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 $C_{\text{max}}$ and AUC, respectively.

**Elimination**
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.

**Pharmacogenomics**
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>
<thead>
<tr>
<th>Dose</th>
<th>Ultrarapid (n=10)</th>
<th>Extensive (n=10)</th>
<th>Intermediate (n=10)</th>
<th>Poor (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 mg (24 h)</td>
<td>600 mg (24 h)</td>
<td>75 mg (Day 5)</td>
<td>150 mg (Day 5)</td>
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<tr>
<td>----------------</td>
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</tr>
<tr>
<td><strong>C</strong>&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>24 (10)</td>
<td>36 (13)</td>
<td>12 (6)</td>
<td>16 (9)</td>
</tr>
<tr>
<td><strong>IPA (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>300 mg (24 h)</td>
<td>40 (21)</td>
<td>39 (27)</td>
<td>13 (7)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
<td>51 (20)</td>
<td>48 (20)</td>
<td>58 (19)</td>
<td>73 (9)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
<td></td>
<td></td>
<td></td>
<td></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>56 (13)</td>
<td>73 (9)</td>
</tr>
<tr>
<td>600 mg (24 h)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>75 mg (Day 5)</td>
<td>20 (10)</td>
<td>24 (10)</td>
<td>39 (14)</td>
<td>39 (14)</td>
</tr>
<tr>
<td>150 mg (Day 5)</td>
<td></td>
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</tr>
</tbody>
</table>

Values are mean (SD)
*Inhibition of platelet aggregation with 5μM 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=2428) and TRITON-TIMI 38 (n=1477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.

**Aspirin**

**Absorption**

Following absorption, the aspirin is hydrolyzed to salicylic acid, with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of aspirin are essentially undetectable 1.5 to 4 hours after dosing. Administration of aspirin with meals did not significantly modify its bioavailability.

**Distribution**

Based on available data, aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations...

**Metabolism and Elimination**

The aspirin is rapidly hydrolyzed by HCE2 (human carboxylesterase 2) in the intestine and the liver to salicylic acid, with a half-life of 0.3 to 0.4 hours for aspirin doses from 75 to 100 mg. This salicylic acid has a plasma half-life of approximately 2 hours. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide and a number of minor metabolites. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations, due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic aspirin doses (10 to 20 g), the plasma half-life may be increased to over 20 hours. At high aspirin doses, the elimination of salicylic acid follows zero-order kinetics (i.e. the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6
hours or higher. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from

Indications

CLOPIVAS-AP is indicated for the prevention of ischemic events, myocardial infarction, stroke and cardiovascular death in patients with acute coronary syndrome.

Dosage And Administration

Prevention of Ischaemic Events

The recommended dose is one tablet once daily.

Acute Coronary Syndrome

Loading dose: Four tablets
Maintenance: One tablet daily

Contraindications

- Hypersensitivity to clopidogrel
- Hypersensitivity to aspirin and/or non-steroidal anti-inflammatory agents
- In patients with the syndrome of asthma with rhinitis and/or nasal polyps
- In patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting)
- Recent history of gastrointestinal bleeding
- Active peptic ulceration or a history of peptic ulceration and those with hemophilia or other clotting disorders or gout

Warnings And Precautions

Drug Interactions

Alcohol
Alcohol may enhance the effects of aspirin on the gastrointestinal tract.

Antacids
Antacids will reduce the effect of aspirin.

Anticoagulants
Aspirin should not be taken concurrently with anti-coagulants. Aspirin may potentiate the action of
heparin and phenindione.

**Warfarin (CYP2C9 Substrates):** Although the administration of clopidogrel 75 mg/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. Aspirin may potentiate the action of warfarin.

**Antiepileptics**
Aspirin may potentiate the action of antiepileptics such as phenytoin, insulin and sulphonylurea hypoglycemic agents.

**Corticosteroids**
Corticosteroids may enhance the effects of aspirin on the gastrointestinal tract.

**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 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.

**Diuretics**
Aspirin adversely affects the action of some diuretics.

**Hypoglycemic Agents**
Aspirin may potentiate the action of insulin and sulphonylurea hypoglycaemic agents.

**Methotrexate**
The toxicity of methotrexate may be enhanced by concomitant use of aspirin.

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**
Coadministration of clopidogrel and NSAIDs increases the risk of gastrointestinal bleeding. Aspirin may potentiate the effects and side effects of other non-steroidal anti-inflammatory drugs to enhance the effects of digoxin.

**Ibuprofen**
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However the limitations of these data and the uncertainties regarding extrapolations of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

**Probenecid**
Aspirin adversely affects the action of probenecid.

### 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.

Avoid concomitant use of CLOPIVAS-AP 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 clopidogrel 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.

### Discontinuation of Clopidogrel

Avoid lapses in therapy, and if CLOPIVAS-AP must be temporarily discontinued, restart as soon as possible. Premature discontinuation of clopidogrel 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.

### Renal Impairment

Aspirin needs to be avoided in patients with severe renal failure (glomerular filtration rate <10 mL/min). Thus, CLOPIVAS-AP should be avoided in patients with impaired renal function.
**Hepatic Impairment**

*CLOPIVAS-AP* should be avoided in patients with impaired hepatic function.

**Pregnancy**

Aspirin is best avoided in late pregnancy and during breast-feeding as it may prolong labour and cause bleeding in the neonate. High doses of aspirin may result in closure of foetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension in the new born. Kernicterus may be a consequence of jaundice in neonates. There are no adequate and well-controlled studies with clopidogrel in pregnant women. Thus, *CLOPIVAS-AP* should be used during pregnancy only if clearly needed.

**Lactation**

Aspirin is best avoided during breast-feeding as it may cause bleeding in the neonate. Aspirin should be avoided during lactation, as there is a risk of Reye's syndrome. Regular use of high doses could impair platelet function and produce hypotherbinaemia in the infant if neonatal vitamin K stores are low. It is not known whether clopidogrel is excreted in human milk. Thus, *CLOPIVAS AP* should be avoided during lactation.

**Pediatric Use**

Aspirin 75 mg is not indicated in children and young people *CLOPIVAS-AP* in the pediatric population have not been established.

**Geriatric Use**

No dosage adjustment is necessary in elderly patients.

**Undesirable Effects**

**Clopidogrel**

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

- Bleeding
- Thrombotic thrombocytopenic purpura

**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=6259)</th>
<th>Placebo (+ aspirin)* (n=6303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding**/**§</td>
<td>3.7%</td>
<td>2.7%</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 (≥ 4 units)</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>1.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Significantly disabling</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Intracerebral bleeding with significant loss of vision</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Requiring 2-3 units of blood</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Minor bleeding¶</td>
<td>5.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* Other standard therapies were used as appropriate.
**/§ Life-threatening and other major bleeding.
¶ 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(+ asprin)(n=22961)</th>
<th>Placebo(+ asprin) (n=22891)</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>
</tbody>
</table>
Fatal 0.2 0.2 0.81
Other noncerebral bleeding (non-major) 3.6 3.1 0.005
Any noncerebral bleeding 3.9 3.4 0.004

*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%, >60 to <70 years = 0.7%, >70 years = 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, >60 to <70 years = 0.6%, >70 years = 0.7%.

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.

**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
- Eye disorders: Eye (conjunctival, ocular, retinal) bleeding
- Gastrointestinal disorders: Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
- General disorders and administration site condition: Fever, hemorrhage of operative wound
- Hepato-biliary disorders: Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness
- Musculoskeletal, connective tissue and bone disorders: Musculoskeletal bleeding, myalgia, arthralgia, arthritis
- Nervous system disorders: Taste disorders, fatal intracranial bleeding, headache
- Psychiatric disorders: Confusion, hallucinations
- Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, respiratory tract bleeding
- Renal and urinary disorders: Increased creatinine levels
- Skin and subcutaneous tissue disorders: Maculopapular or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme, skin bleeding, lichen planus, generalized pruritus
Aspirin produces a prolongation of the bleeding time and may produce epigastric distress, nausea and vomiting, gastric or duodenal ulcers and erosive gastritis which may lead to serious gastrointestinal bleeding. These side effects are more likely to occur when higher doses are administered, although they may also occur when low doses are used.

Oesophagitis, oesophageal ulceration, perforation. Erosive gastritis, erosive duodenitis, gastroduodenal ulcer/perforations, upper gastro-intestinal symptoms such as gastralgia. Small (jejenum and ileum) and large (colon and rectum) intestinal ulcers, colitis and intestinal perforation. These reactions may or may not be associated with haemorrhage, and may occur at any dose of acetylsalicylic acid and in patient with or without warning symptoms or a previous history or serious GI events.

Iron deficiency anemia may develop as a result of occult gastrointestinal bleeding when aspirin is used for long periods of time.

Aspirin may cause intracranial haemorrhage.

Aspirin may cause haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

Aspirin may cause tinnitus, dizziness, vertigo or hearing loss.

Aspirin sensitivity is most commonly manifested by asthma, vasomotor rhinitis, urticaria, angioneurotic edema and allergic dermatological reactions, hypoglycaemia, gout. As well as anaphylactic shock, aggravation of allergic symptoms of food allergy.

Aspirin may cause an elevation of hepatic enzymes, liver injury, mainly hepatocellular.

Low doses of aspirin have been reported to cause retention of uric acid, whereas high dosage may increase excretion.

Aspirin may cause acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics).

Respiratory, thoracic and mediastinal disorder; non-cardiogenic pulmonary edema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid.

Clopidogrel

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.

Aspirin

Salicylate poisoning is usually associated with plasma concentrations ≥350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Common features of salicylate poisoning include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier. Uncommon features of salicylate poisoning include hematemesis, hyperpyrexia, hypoglycemia, hypokalemia, thrombocytopenia, increased INR/PTT, intravascular coagulation, renal failure and non-cardiac pulmonary edema.

Central nervous system features including confusion, disorientation, coma and convulsions, are less common in adults than in children.

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate.

The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary edema. Hemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations≥700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Packaging Information

**CLOPIVAS-AP** 75: Strip of 10 tablets  
**CLOPIVAS-AP** 150: Strip of 10 tablets

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CLOPIVAS-AP Tablets

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