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-AP 75
Each uncoated bilayered tablet contains:
Clopidogrel (as bisulfate) ...... 75 mg
and Aspirin IP ........... 75 mg
CLOPIVAS-AP 150
Each uncoated bilayered tablet contains:
Clopidogrel (as bisulfate) ...... 75 mg
and Aspirin IP ........... 150 mg

Dosage Form

Tablet

Description

CLOPIVAS-AP is a fixed-dose combination of 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 P2Y₁₂ 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 P2Y₁₂ receptor and the subsequent ADP-mediated activation of the 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. 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 Cₘₐₓ. Similar results were observed when a clopidogrel 300 mg loading dose was administered with a high-fat breakfast.

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

The $C_{\text{max}}$ 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.

**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.

**Aspirin**
Absorption
Non ionised acetylsalicylic acid is absorbed from the stomach. There is also absorption of acetylsalicylates from the intestines.

Distribution
Aspirin appears rapidly in all body tissues. It does cross the placenta and appears in breast milk and it is moderately bound to plasma proteins.

Excretion
Excretion is a salicylic acid and as compounds in the urine and increases as the pH rises.

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 clopidogrel 300 mg followed by 75 mg per day and clopidogrel 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></th>
<th>Dose</th>
<th>Ultrarapid (n=10)</th>
<th>Extensive (n=10)</th>
<th>Intermediate (n=10)</th>
<th>Poor (n=10)</th>
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<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</strong></td>
<td>300 mg (24 h)</td>
<td>24 (10)</td>
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<tr>
<td></td>
<td>600 mg (24 h)</td>
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<td>49 (23)</td>
<td>56 (22)</td>
<td>32 (25)</td>
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<tr>
<td></td>
<td>75 mg (Day 5)</td>
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<td>58 (19)</td>
<td>60 (18)</td>
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<tr>
<td></td>
<td>150 mg (Day 5)</td>
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<td>74 (14)</td>
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<td>39 (14)</td>
<td>50 (16)</td>
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<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 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.

**Indications**

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

Unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI) in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death or refractory ischemia). Combination of clopidogrel + aspirin is indicated for the treatment of ACS whether or not patients undergo cardiac revascularisation (surgical or PCI, with or without stent).

ST-segment elevation acute myocardial infarction (STEMI) in order to prevent atherothrombotic events. In this population, clopidogrel + aspirin 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 in medically treated patients eligible for thrombolytic therapy.

**Dosage And Administration**

- **Prevention of Ischemic Events**
  
  The recommended dose is one tablet of CLOPIVAS-AP once daily.

- **Acute Coronary Syndrome**
  
  Loading dose: Four tablets of CLOPIVAS-AP 75
  Maintenance dose: One tablet of CLOPIVAS-AP 75/150 daily

- **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 clopidogrel. 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**

- Hypersensitivity to clopidogrel, salicylates or any of the excipients or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Severe hepatic impairment.
- Severe renal impairment
- Active pathological bleeding such as hemophilia, intracranial hemorrhage, gastrointestinal bleeding or other kinds of bleeding such as cerebrovascular hemorrhages.
- Active peptic ulceration or past history of ulceration or dyspepsia.
- Patients who are suffering from gout.
- Third trimester of pregnancy.
- Concurrent anticoagulant therapy should be avoided.
- Nasal polyps associated with asthma (high risk of severe sensitivity reactions).
- Aspirin doses >100 mg/day during the third trimester of pregnancy; Methotrexate used at doses >15mg/week.

**Warnings And Precautions**

- **General**

  *General Risk of Bleeding*
  
  Clopidogrel
  
  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.

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.

Aspirin
There is an increased risk of hemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

Aspirin 75 mg is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin 75 mg is to be used with caution in cases of hypertension and when patients have a past history of gastric or duodenal ulcer or hemorrhagic episodes or are undergoing therapy with anticoagulants.

Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

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

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.

Drug Interactions

Clopidogrel

**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
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 when esomeprazole 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. 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.

Aspirin

**Anticoagulants (e.g. coumarin, heparin, warfarin):** Concomitant administration of two agents increase the risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. Bleeding time should be monitored.

**Anti-platelet Agents (e.g. clopidogrel and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine):** Addition of these agents increase the risk of gastrointestinal bleeding.

**Antidiabetics (e.g. sulphonylureas):** Salicylics may increase the hypoglycemic effect of sulphonylureas.

**Digoxin and Lithium:** Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

**Diuretics and Antihypertensives:** NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency. Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

**Carbonic Anhydrase Inhibitors (e.g. acetazolamide):** May result in severe acidosis and increased central nervous system toxicity.

**Systemic Corticosteroids:** The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered.

**Methotrexate (used at doses <15 mg/week):** The combined drugs, methotrexate and acetylsalicylic acid, may increase hematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

**Other NSAIDs:** Increased risk of ulcersation and gastrointestinal bleeding due to synergistic effects.

**Valproate:** Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

**Phenytoin:** Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

**Ibuprofen:** Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation 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.

**Ciclosporin, tacrolimus:** Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

**Alcohol:** Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

**Antacids:** Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

**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.

### Renal Impairment

Experience with clopidogrel is limited in patients with severe and moderate renal impairment. Aspirin needs to be avoided in patients with severe renal failure (glomerular filtration rate < 10 mL/min). Aspirin should be used with caution in patients with moderately impaired renal function or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function.

### Hepatic Impairment

Dose adjustment of clopidogrel is not necessary in patients with hepatic impairment. Aspirin needs to be avoided in patients with severe hepatic impairment. Aspirin should be used with caution in patients with moderately impaired hepatic function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

### Pregnancy

**Category C**

**Clopidogrel**

There are no adequate and well-controlled studies with clopidogrel in pregnant women. Clopidogrel should be used during pregnancy only if clearly needed.

**Aspirin**

Low doses (up to 100 mg/day): Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100-500 mg/day: There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above: Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastrochisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
- the mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

### Lactation

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 clopidogrel, taking into account the importance of the drug to the mother.

Low quantities of salicylates and of their metabolites are excreted into the breast milk. Since adverse effects for the infant have not been reported up to now, short-term use of the recommended dose does not require suspending breastfeeding. In cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued.

Pediatric Use

Safety and effectiveness of clopidogrel in the pediatric population have not been established. Aspirin is not recommended for use in adolescents/children under 16 years unless the expected benefits outweigh the risks. Acetylsalicylic acid may be a contributory factor in the causation of Reye's Syndrome in some children.

Geriatric Use

No dosage adjustment of clopidogrel is necessary in elderly patients. Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Undesirable Effects

Clopidogrel

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=6259)</th>
<th>Placebo (+ aspirin)* (n=6303)</th>
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<tbody>
<tr>
<td>Major bleeding²⁰⁰</td>
<td>3.7⁶</td>
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<tr>
<td>Type of bleeding</td>
<td>Clopidogrel (+ aspirin) (n=22961)</td>
<td>Placebo (+ aspirin) (n=22891)</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Major noncerebral or cerebral bleeding *<em>/</em></td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Major noncerebral</td>
<td>0.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

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

Major bleeding event rate for clopidogrel + aspirin was dose-dependent on aspirin: <100 mg = 2.6%; 100-200 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 = 2.0%; 100-200 mg = 2.3%; >200 mg = 4.0%
Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, 65 to <75 years = 3.1%, >75 years = 3.6%

† Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.
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).
Fatal | 0.2 | 0.2 | 0.90
--- | --- | --- | ---
Hemorrhagic stroke | 0.2 | 0.2 | 0.91
Fatal | 0.2 | 0.2 | 0.81
Other noncerebral bleeding (non-major) | 3.6 | 3.1 | 0.005
Any noncerebral bleeding | 3.9 | 3.4 | 0.004

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.

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 condition: Fever, hemorrhage of operative wound.

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

Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness

Musculoskeletal, connective tissue and bone disorders: Musculoskeletal bleeding, myalgia, arthralgia, arthritis

Nervous system disorders: Taste disorders, fatal intracranial bleeding, headache

Psychiatric disorders: Confusion, hallucinations

Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, respiratory tract bleeding, eosinophilic pneumonia

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

Vascular disorders: Vasculitis, hypotension

Aspirin

Side effects are grouped on the basis of System Organ Class. Within each system organ class the frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data)

| Blood and lymphatic system disorders | Common: Increased bleeding tendencies.  
|                                    | Rare: Thrombocytopenia, granulocytosis, aplastic anemia.  
|                                    | Not known: Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (hematemesis, melena) or occult gastrointestinal bleeding, which may lead to iron deficiency anemia (more common at higher doses). |
| Immune system disorders | Rare: Hypersensitivity reactions, angio-edema, allergic edema, anaphylactic reactions including shock. |
| Metabolism and digestive system disorders | Not known: Hyperuricemia. |
| Nervous system disorders | Rare: Intracranial hemorrhage  
| | Not known: Headache, vertigo. |
| Ear and labyrinth disorders | Not known: Reduced hearing ability; tinnitus. |
| Vascular disorders | Rare: Hemorrhagic vasculitis. |
| Respiratory, thoracic and mediastinal disorders | Uncommon: Rhinitis, dyspnea.  
| | Rare: Bronchospasm, asthma attacks. |
| Reproductive system and mammary disorders | Rare: Menorrhagia |
### Gastrointestinal disorders

**Common:**
- Dyspepsia.

**Rare:**
- Severe gastrointestinal hemorrhage, nausea, vomiting.

**Not known:**
- Gastric or duodenal ulcers and perforation, diarrhea.

### Hepatobiliary disorders

**Not known:**
- Hepatic insufficiency

### Skin and subcutaneous tissue disorders

**Uncommon:**
- Urticaria.

**Rare:**
- Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.

### Renal and urinary tract disorders

**Not known:**
- Impaired renal function, salt and water retention.

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

## Overdosage

### 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/PT, 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.

### Incompatibility

Clopidogrel: Not applicable  
Aspirin: None stated  

### Shelf-Life

Two year

### Storage And Handling Instructions

Store in cool dry place. Protect from moisture.

### Packaging Information

CLOPIVAS-AP 75: Strip of 15 tablets  
CLOPIVAS-AP 150: Strip of 15 tablets  

Last Updated: April 2017  
Last Reviewed: April 2017

CLOPIVAS-AP Tablets

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