

omeprazole or esomeprazole should be discouraged. Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole. The plasma concentrations of the active metabolite were 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole. There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers (except cimetidine which is a CYP2C19 inhibitor) or antacids interfere with antiplatelet activity of clopidogrel. 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, ACEi, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antiplatelet agents (including insulin), antiplatelet agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

**FERTILITY, PREGNANCY AND LACTATION :**

**Pregnancy**  
As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

**Breastfeeding**

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel.

**Fertility**

Clopidogrel was not shown to alter fertility in animal studies.

**UNDESIRABLE EFFECTS :**

Clopidogrel has been evaluated for safety in more than 44,000 patients who have participated in clinical studies, including over 12,000 patients treated for 1 year or more. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY, COMMIT and ACTIVE-A studies. In addition to clinical studies experience, adverse reactions have been spontaneously reported. Bleeding is the most common reaction reported in clinical studies where it was mostly reported during the first month of treatment. Adverse reactions are presented in the table below. Their frequency is defined using the following conventions: 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). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system disorders	Thrombocytopenia, leukopenia, eosinophilia	Thrombocytopenia, leukopenia, neutropenia, including severe neutropenia	Neutropenia, Thrombotic/thrombotic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia	
Immune system disorders			Serum sickness, anaphylactoid reactions	
Psychiatric disorders			Hallucinations, confusion	
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, dizziness, disorientation		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis		Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis	
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastro- and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retropositional haemorrhage	Gastrointestinal and retropositional haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders			Acute liver failure, hepatitis, abnormal liver function test	
Skin and subcutaneous tissue disorders	Pruritus	Rash, pruritus, skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal connective tissue and bone disorders			Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia	
Renal and urinary disorders		Haematuria	Glomerulonephritis, blood creatinine increased	
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

**OVERDOSE:**

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

**PRECLINICAL SAFETY DATA :**

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and was a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose. At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon. There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day). Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies, and showed no genotoxic activity. Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

**PRESENTATION:**

Blister pack of 10's & HDPE pack of 1000's

**STORAGE:**  
STORE UP TO 30°C.  
KEEP OUT OF REACH OF CHILDREN.

**Zydus Cadila**

Manufactured by:  
Cadila Healthcare Limited,  
Kundaim Industrial Estate,  
Plot No. 202-213, Kundaim,  
Goa - 403 115, India.

For the use of a Registered Medical practitioner or a Hospital or a Laboratory only.

**NOKLOT CLOPIDOGREL TABLETS USP 75MG**

**COMPOSITION:**

Each film coated tablet contains:  
Clopidogrel Bisulfate USP  
Equivalent to Clopidogrel 75mg  
Colors: Titanium Dioxide, FD&C Yellow #6, FD&C Red #40

**DESCRIPTION:**

Clopidogrel bisulfate is an inhibitor of ADP induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically it is methyl 2-(3,4-dihydro-2H-pyridine-5(1H)-one-2-thiolate) sulfonamide (1:1). The empirical formula of clopidogrel bisulfate is C<sub>16</sub>H<sub>16</sub>ClNO<sub>2</sub>S<sub>2</sub> and its molecular weight is 419.9.

**CLINICAL CHARACTERISTICS:**

**Pharmacodynamic properties:**

**Pharmacotherapeutic group:** Platelet aggregation inhibitors excl. Heparin.

**ATC Code:** B01AC-04

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y<sub>12</sub> receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP. Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day, this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

The safety and efficacy of clopidogrel have been evaluated in 5 double-blind studies involving over 88,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, COMMIT and ACTIVE-A studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease. The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75 mg/day or ASA 325 mg/day and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction. Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p=0.045), which corresponds, for every 1,000 patients treated for 2 years, to 10 (CI: 0 to 20) additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at p=0.003) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%, CI: 8.9 to 38.2) and weaker (not significantly different from ASA) in stroke patients (RRR = 7.3%, CI: -8.7 to 18.1 [p=0.258]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR = -4.0%, CI: -22.5 to 11.7 [p=0.639]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤75 years, since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

**Acute coronary syndrome**

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes and troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, N=6,259) or placebo (N=6,303), both given in combination with ASA (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 82.6% patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel and placebo was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint (cardiovascular (CV) death, myocardial infarction (MI), or stroke) was 82 (0.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%, p=0.0009) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel-ASA group was not further increased, whereas the risk of haemorrhage persisted.

The use of clopidogrel in CURE was associated with a decrease in the need of thrombolytic therapy (RRR = 43.3%, CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%, CI: 6.5%, 28.3%). The number of patients experiencing the secondary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel-treated group and 1,187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the clopidogrel-treated group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI (27 (4.6%) in the clopidogrel treated group and 363 (5.8%) in the placebo treated group). There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data show that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering medicinal products, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily). In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel had been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1,752) or placebo (n=1,739), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the pre-discharge angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients aged ≥ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 66.5% heparin, 78.7% beta blockers, 54.9% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint, representing an absolute reduction of 6.7% and a 36 % odds reduction in favor of clopidogrel (95% CI: 24, 47%; p < 0.001), mainly related to a reduction in the incidence of re-occluded infarcted arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day, n=22,991) or placebo (n=22,891), in combination with ASA (162 mg/day), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.5% women, 58.4% patients ≥ 60 years (26% ≥ 70 years) and 54.5% patients who received fibrinolytics. Clopidogrel significantly reduced the relative risk of death from any cause by 7% (p=0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p=0.002), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

**Atrial fibrillation**

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment. The ACTIVE-W study demonstrated that anticoagulant treatment with vitamin K antagonists was more effective than with clopidogrel and ASA.

The ACTIVE-A study (N=7,554) was a multicenter, randomized, double-blind, placebo-controlled study which compared clopidogrel 75 mg/day + ASA (N=3,772) to placebo + ASA (N=3,782). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and at least one of the following risk factors: age ≥75 years or age ≥55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease, treated for

280 mm

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180 mm