CLOVELEN®

Clopidogrel besilate

Clovelen® Film coated tablets 75mg/tab: Pink, round, biconvex, film coated tablets in blister packs of 7 tablets. Packs of 28 tablets.
Composition: Active Ingredients: Clopidogrel besilate.
Excipients: *Core:* Cellulose microcrystalline, Spray-dried mannitol, Hydroxypropylcellulose, Crospovidone, Citric acid, Polyethylene glycol, Stearic acid, Talc.
Coating: Hypromellose (E421), Iron oxide red (E172), Lactose monohydrate, Triacetin (E1518), Titanium dioxide (E171).

Pharmacology

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its respective platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day. This inhibition increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 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 4 double-blind studies involving over 80,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Indications

Clovelen® is indicated in adults for the prevention of atherothrombotic events in:
• Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

Recommended Dosage and Administration

• Adults and elderly
Clovelen® should be given as a single daily dose of 75 mg with or without food.
• Children
The safety and efficacy of clopidogrel in children and adolescents have not yet been established.
• Renal impairment
Therapeutic experience with clopidogrel is limited in patients with renal impairment.
• Hepatic impairment
Therapeutic experience with clopidogrel is limited in patients with moderate hepatic disease who may have bleeding diatheses.

Pharmacogenetics

CYP2C19 poor metaboliser status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolisers should be determined.

Side effects

Clopidogrel has been evaluated for safety in more than 42,000 patients who have participated in clinical studies, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies are discussed below. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported. Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment. In CAPRIE study, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was 1.4% for clopidogrel and 1.6% for ASA. In CURE study, the major bleeding event rate for clopidogrel + ASA was dose-dependent on ASA (<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo + ASA (<100mg: 2.0%; 100-200mg: 2.3%; >200mg: 4.0%). The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months (clopidogrel: 9.6%; placebo: 6.6%), 1-3 months (clopidogrel: 4.5%; placebo: 2.3%), 3-6 months (clopidogrel: 3.8%; placebo: 1.6%), 6-9 months (clopidogrel: 3.2%; placebo: 1.5%), 9-12 months (clopidogrel: 1.9%; placebo: 1.0%). There was no excess in major bleeds with clopidogrel + ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel + ASA vs. 5.3% placebo + ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + ASA, and 6.3% for placebo + ASA. In CLARITY study, there was an overall increase in bleeding in the clopidogrel + ASA group (17.4%) vs. the placebo + ASA group (12.9%).The incidence of major bleeding was similar between groups (1.3% versus 1.1% for the clopidogrel + ASA and the placebo + ASA groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy. In COMMIT study, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups (0.6% versus 0.5% in the clopidogrel + ASA and the placebo + ASA groups, respectively).
Adverse reactions that occurred either during clinical studies or that were spontaneously reported 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 drug reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and the lymphatic system				

System Organ Class	Common	Uncommon	Rare	Very rare
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal 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	Bruising	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				Musculoskeletal 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		

Contra-Indications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

Use in Pregnancy and Lactation

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/foetal development, labour or postnatal development.
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.

Drug Interactions

Oral anticoagulants: The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings.
Glycoprotein IIb/IIIa inhibitors: Clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors.
Acetylsalicylic acid (ASA): ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and ASA have been administered together for up to one year.
Heparin: In a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.
Thrombolytics: The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution.
Other concomitant therapy: 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 coadministration of phenobarbital, cimetidine, 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 studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P450 2C9. This could potentially lead to increased plasma levels of medicinal products such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by Cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide 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, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions. Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of medicinal products that inhibit CYP2C19 should be discouraged. Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.
Proton Pump Inhibitors (PPI)
In a crossover clinical study, clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 45% (Day 1) and 40% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) with 5μM ADP was diminished by 39% (24 hours) and 21% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole 12 hours apart did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Esomeprazole is expected to give a similar interaction with clopidogrel.
Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprozole should be discouraged. No conclusive data on the pharmacodynamic interaction of clopidogrel and other PPIs are available. 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.

Storage conditions: Clovelen® film coated tablets should be stored in temperature below 25°C, in a dry place.

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