SUMMARY OF PRODUCT CHARACTERISTICS

ONECLAPZ 75

Clopidogrel Tablets 75 mg

NAME OF THE MEDICINAL PRODUCT : Clopidogrel Tablets 75 mg

(TRADE) NAME OF THE PRODUCT : ONCLAPZ 75

STRENGTH : 75 mg

Route of administration : Oral

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:
Clopidogrel bisulphate Equivalent to Clopidogrel Tablets 75 mg.

PHARMACEUTICAL FORM
Clopidogrel Tablets 75 mg:
Pink colored, round, biconvex, beveled edge, film-coated tablets debossed with 'E' on one side and '34' on the other side.

CLINICAL PARTICULARS
Therapeutic indications
Prevention of atherothrombotic events, Clopidogrel is indicated in:
- Adult 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.
- Adult patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention.
  - ST segment elevation acute myocardial infarction, in combination with acetylsalicylate acid (ASA) in medically treated patients eligible for thrombolytic therapy.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation
In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

Posology and method of administration
Adults and older people
Clopidogrel should be given as a single daily dose of 75mg.
In patients suffering from acute coronary syndrome:
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): Clopidogrel treatment should be initiated with a single 300mg loading dose and then continued at 75mg once a day (with acetylsalicylic acid (ASA) 75mg-325mg daily). Since higher doses of ASA were associated with higher bleeding risk, it is recommended that the dose of ASA should not be higher than 100mg. The optimal duration of treatment has not been formally established.
- ST segment elevation acute myocardial infarction: Clopidogrel should be given as a single daily dose of 75mg initiated with a 300mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age, Clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks.

In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel.

If a dose is missed:
- Within less than 12 hours after regular scheduled time, patient should take the dose immediately and then take the next dose at the regular scheduled time.
- For more than 12 hours, patients should take the next dose at the regular scheduled time and should not double the dose.

Paediatric population: Clopidogrel should not be used in children because of efficacy concerns.

Renal impairment: Therapeutic experience is limited in patients with renal impairment (see section Special warnings and precautions for use).

Hepatic impairment: Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section Special warnings and precautions for use).

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

Warnings and Precautions
Bleeding and haematological disorders
Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section Undesirable effects). As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs). Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section Interaction with other medicinal products and other forms of interaction).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

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

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

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

Recent ischaemic stroke
In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

Cytochrome P450 2C19 (CYP2C19)
Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

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 strong or moderate CYP2C19 inhibitors should be discouraged (see section Interaction with other medicinal products and other forms of interaction for a list of CYP2C19 inhibitors, see also section Pharmacokinetic properties).

CYP2C8 substrates
Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section Interaction with other medicinal products and other forms of interaction).

Cross-reactions among thienopyridines
Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section Undesirable effects). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Renal impairment
Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients (see section Posology and method of administration).

Hepatic impairment
Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section Posology and method of administration).

This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

Special warnings and special precautions for use

Pharmacogenetics:

Based on literature data, patients with genetically reduced CYP22C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.

Interactions with Other Medicaments

Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section Special warnings and precautions for use). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised 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.

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section Special warnings and precautions for use).

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 (see section Special warnings and precautions for use). However, clopidogrel and ASA have been administered together for up to one year (see section Pharmacodynamic properties).

Heparin: 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 (see section Special warnings and precautions for use).

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 (see section Undesirable effects).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): 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(see section Special warnings and precautions for use).

SSRIs: since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

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A/s : 165 x 280 mm Black

AUROBINDO Packaging Development	Product Name: Oneclapz 75	Component: Leaflet	Item Code: P1536240	Date & Time: 17.01.2024 & 12:10 PM
	Customer / Country: Malaysia U3	Version No.: 00	Reason Of Issue: Submission	Reviewed / Approved by
Team Leader: Kiran kumar	Dimensions: 165 x 280 mm	No. Colours : 01		
Initiator: Shirisha				
Artist: SCD	Pharmacode: 36240	36240		
Additional Information : Supersede code: P1513800				Sign / Date

Interaction with other medicinal products and other forms of interaction: 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 and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g. proton pump inhibitors) should be discouraged.

Pregnancy and lactation

Pregnancy
It is preferable not to use Clopidogrel during pregnancy as a precautionary measure.

Lactation

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

Side Effects
Blood and lymphatic system disorders:

- Uncommon: Thrombocytopenia, leucopenia, eosinophilia
- Rare: Neutropenia, including severe neutropenia
- Very rare: Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia.

Cardiac disorders
- Very rare: Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel.

Immune system disorders:
- Very rare: Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel).

Psychiatric disorders:
- Very rare: Confusion, Hallucinations

Nervous system disorders:
- Uncommon: Intracranial bleeding, headache, paraesthesia, dizziness
- Very rare: Taste disturbances

Eye disorders:
- Uncommon: Eye bleeding (conjunctival, ocular, retinal)

Ear and labyrinth disorders:
- Rare: Vertigo

Vascular disorders:
- Common: Haematoma
- Very rare: Serious haemorrhage, haemorrhage of operative wound, vasculitis, Hypotension

Respiratory, thoracic and mediastinal disorders:
- Common: Epistaxis
- Very rare: Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Gastrointestinal disorders:
- Common: Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia
- Uncommon: Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence.
- Rare: Retroperitoneal haemorrhage
- Very rare: Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis

Hepato-biliary disorders:
- Very rare: Acute liver failure, hepatitis, abnormal liver function test

Skin and subcutaneous tissue disorders:
- Common: Bruising
- Uncommon: Rash, pruritus, skin bleeding (purpura)
- Very rare: Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus.

Reproductive systems and breast disorders:
- Rare: Gynaecomastia

Musculoskeletal, connective tissue and bone disorders:
- Very rare: Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, Myalgia

Renal and urinary disorders:
- Uncommon: Haematuria
- Very rare: Glomerulonephritis, blood creatinine increased

General disorders and administration site conditions:
- Common: Bleeding at puncture site
- Very rare: Fever

Investigations:
- Uncommon: 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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: platelet aggregation inhibitors excl. Heparin

Mechanism of action:
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 P2Y12 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.

Pharmacokinetic properties
Absorption
After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Distribution
Clopidogrel and the main circulating (inactive) metabolite bind reversibly to human plasma proteins (98% and 94% respectively). The binding is non-saturable over a wide concentration range.

Biotransformation
Clopidogrel is extensively metabolised by the liver. Clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised 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. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.
The Cmax 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. Cmax occurs approximately 30 to 60 minutes after dosing.

Elimination
Following an oral dose of 14C-labelled clopidogrel, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Pharmacogenetics
The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19.
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.

Special populations
The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Renal impairment
After repeated doses of 75 mg clopidogrel per day in patients with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy patients, however, the prolongation of bleeding time was similar to that seen in healthy patients receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment
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 patients.

Race
The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity.

PHARMACEUTICAL PARTICULARS
List of Excipients
Microcrystalline Cellulose, Mannitol, Hydroxypropyl cellulose Low substituted, Crospovidone, Macrogol 6000, Hydrogenated Castor oil and Opadry II pink.

Incompatibilities
None known.

Shelf life
2 years.

Special precautions for storage
Store in a dry place below 30 °C.

Nature and contents of container
Blister Pack: Blister of 3 x 10tablets.

Manufactured By:

AUROBINDO

Aurobindo Pharma Ltd.,
Unit III, Survey No. 313 & 314, Bachupally village,
Bachupally Mandal, Medchal- Malkajgiri district,
Telangana state, India.

Product Registration Holder
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