SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

APLATIN 75
Clopidogeral Tablets USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Clopidogrel Bisulfate USP
Eq. to Clopidogrel : 75 mg
Excipients : Q.S.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet
For oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APLATIN 75 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, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with 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.

4.2 Posology and method of administration

Adults and Older people
APLATIN 75 should be given as a single daily dose of 75 mg.

In patients suffering from acute coronary syndrome:
Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction):

- **APLATIN 75** treatment should be initiated non-Q-wave myocardial infarction), clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg 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 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.
- ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg 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. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting .

Adult patients with moderate to high-risk TIA or minor IS:
Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA (75 mg -100 mg once daily). Treatment with clopidogrel and ASA should be started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy.
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.

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

Renal impairment
Therapeutic experience is limited in patients with renal impairment.

Hepatic impairment
Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses

Method of administration:
Oral

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
- Patients who are using Repaglinide
- Patients with significant liver impairment or cholestatic jaundice

4.4 Special warnings and precautions for use

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.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of Clopidogrel.

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.

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.

Renal impairment
Therapeutic experience with Clopidogrel is limited in patients with renal impairment. Therefore Clopidogrel should be used with caution in these patients.

Cross-reactivity among thienopyridines

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see ADVERSE REACTIONS). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological 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 cross-reactivity is advised.

Use with Proton Pump Inhibitors (PPI):
Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of CLOPIDOGREL. Avoid use of strong or moderate CYP2C19 inhibitors with CLOPIDOGREL. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity, or alternative treatment strategies. Pantoprazole, a weak CYP2C19 inhibitor, had less effect on the pharmacological activity of CLOPIDOGREL than omeprazole.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk 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 bleedings.

Glycoprotein IIb/IIIa inhibitors: Clopidogrel should be used with caution in patients who 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.

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.

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.

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 was not modified by the co-administration of Clopidogrel. Antacids did not modify the extent of Clopidogrel absorption.

4.5 Pregnancy and lactation

Pregnancy
As no clinical data on exposure to Clopidogrel during pregnancy are available.

Lactation
It is unknown whether Clopidogrel is excreted in human breast milk. Animal studies have shown excretion of Clopidogrel in breast milk.

4.7 Effects on ability to drive and use machines

Clopidogrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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), not known (cannot be estimated from the available data).Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Blood and the lymphatic system disorders
Thrombocytopenia, leucopenia, eosinophilia, Neutropenia, including severe Neutropenia, Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia,

Acquired haemophilia, granulocytopenia, anaemia.

Immune system disorders

Serum sickness, anaphylactoid reactions, Crossreactive drug hypersensitivity among thienopyridines.

Psychiatric disorders

Hallucinations, confusion

Nervous system disorders

Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness, 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, eosinophilic pneumonia

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

Reproductive systems and breast disorders

Gynaecomastia

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

4.9 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.
A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and rats, and at 3000 mg/kg to baboons.

Treatment:
No antidote to the pharmacological activity of clopidogrel has been found. Platelet transfusion may be used to reverse the pharmacological effects of CLOPIDOGREL when quick reversal is required.
For management of a suspected drug overdose, contact your regional Poison Control Centre.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors
ATC code: B01AC-04

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 GP IIb/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.

5.2 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 mg/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 in vitro to human plasma proteins (98% and 94% respectively). The binding is non-saturable in vitro over a wide concentration range.

Biotransformation
Clopidogrel is extensively metabolised by the liver. In vitro and in vivo, 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.

Elimination
Following an oral dose of 14C-labelled Clopidogrel in man, 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.

5.3 Preclinical safety data

Clopidogrel has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse events observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

Clopidogrel was well tolerated compared to aspirin in a large controlled clinical trial (CAPRIE). The overall tolerability of clopidogrel in this study was similar to aspirin, regardless of age, gender and race. The clinically relevant adverse events observed in CAPRIE, CURE, CLARITY and COMMIT.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Name of Ingredients	Specification
Maize Starch	BP
Micro Crystalline Cellulose	BP
Colloidal Anhydrous silica	BP
Povidone	BP
Magnesium Stearate	BP
Sodium Bicarbonate	BP
Sodium starch Glycolate	BP
Hydrogenated Castor oil	BP
Red Oxide of Iron	IHS
Titanium Dioxide	IHS
Methylene Chloride	BP
Isopropyl Alcohol	BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

24 Months

6.4 Special Precautions for Storage

Store below 30ºC in a cool and dry place. Protect from heat, light and moisture.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and Contents of Container

3 × 10 Alu-Alu Blister Pack.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ahmedabad
Gujarat, India.
E-mail: info@sagalabs.com
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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

06665/07972/NMR/2019

9. DATE OF FIRSHT AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/10/2021

10. DATE OF REVISION OF THE TEXT

01 April 2026