INSTACLOP 75 Clopidogrel Tablets USP 75 mg	
Module 1	Administrative Information and Product Information
Section 1.6	Product Information

1.6.1 Prescribing information (Summary of Product Characteristics)

Please find enclosed herewith SmPC.

Summary of Product Characteristics
(Product Data Sheet)

1.	**Name of the Medical Product**
	Instaclop 75 **Clopidogrel Tablets USP 75mg**
	1.1 Strength : Each film coated Tablet contains: Clopidogrel Bisulphate USP equivalent to Clopidogrel……75 mg Colour: Red Oxide of Iron and Titanium Dioxide
	1.2 Pharmaceutical Dosage Form : Tablets
2.	**Qualitative & Quantitative Composition**

Ingredients	Specifications	Quantity per tablet
Clopidogrel Bisulphate	USP	97.875*mg
Polyethylene Glycol 6000	USP-NF	2.50mg
Purified water	#	q.s
Isopropyl Alcohol	BP	q.s
Microcrystalline Cellulose	BP	27.625mg
Low-substituted Hydroxy Propyl Cellulose	USP-NF	15.00mg
Mannitol	BP	100.00mg
Hydrophobic Colloidal Silica	USP-NF	2.00mg
Sodium Stearyl Fumarate	USP-NF	5.00mg
Wincoat WT-1274	IH	7.50mg**
Isopropyl Alcohol	BP	q.s
Dichloromethane	BP	q.s

* Clopidogrel Bisulphate 97.875mg equivalent to Clopidogrel 75mg
# Purified water conforms to the specification of IP/BP/USP/Ph.Eur./IH
** 40.0% Extra to compensate losses during coating.
USP: United States Pharmacopeia
USP-NF: United States Pharmacopeia – National Formulary
IH : In-house specification
BP : British Pharmacopoeia

3.	**Pharmaceutical Form:** Light Pink coloured, circular, biconvex film coated tablets.

4. Clinical Particulars

4.1 Therapeutic Indications:

Clopidogrel is indicated for the reduction of atherothrombotic events as follows:

- Recent MI, Recent Stroke or Established Peripheral Arterial Disease

  For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Clopidogrel has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.
- Acute Coronary Syndrome

  For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, Clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

  For patients with ST-segment elevation acute myocardial infarction, Clopidogrel 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. This benefit is not known to pertain to patients who receive primary angioplasty.

4.2 Posology and Method of administration:

- **Recent MI, Recent Stroke, or Established Peripheral Arterial Disease**

  The recommended daily dose of Clopidogrel is 75 mg once daily.

- **Acute Coronary Syndrome**

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q wave MI), Clopidogrel should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with Clopidogrel.

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of Clopidogrel is 75 mg once daily, administered in combination with aspirin, with or without

4.3 Method of administration:

For oral use

4.4 Contraindications:

The use of Clopidogrel is contraindicated in the following conditions:

- Hypersensitivity to the drug substance or any component of the product.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.5 Special warning and precautions for use:

Reduced effectiveness due to impaired CYP2C19 function:

The inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. Clopidogrel is metabolized to this active metabolite in part by CYP2C19. This metabolism can be impaired by genetic variations in CYP2C19 and by concomitant medications that interfere with CYP2C19. Avoid use of Clopidogrel in patients with impaired CYP2C19 function due to known genetic variation or due to drugs that inhibit CYP2C19 activity.

Genetic variations: Patients with genetically reduced CYP2C19 function have diminished antiplatelet responses and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.

Thrombotic thrombocytopenic purpura (TTP):

TTP has been reported rarely following use of Clopidogrel, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, micro-angiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.

General:

Clopidogrel prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, Clopidogrel should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment.

In patients with recent TIA or stroke who are at high risk of 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.

GI Bleeding:

Clopidogrel should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking Clopidogrel.

Use in Hepatic-Impaired Patients:

Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel should be used with caution in this population.

Use in Renal-Impaired Patients:

Experience is limited in patients with severe renal impairment. Clopidogrel should be used with caution in this population.

4.6 Paediatric population

Safety and effectiveness in the pediatric population have not been established.

4.7 Interactions with other medicinal products and other forms of Interactions :

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant use of drugs that inhibit CYP2C19, including omeprazole, esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

Omeprazole: Co-administration of Clopidogrel with omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of Clopidogrel if given concomitantly or if given 12 hours apart. There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers (except cimetidine, which is a CYP2C19 inhibitor) or antacids interfere with the antiplatelet activity of clopidogrel.

Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by Clopidogrel. Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, 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 inhibition of platelet aggregation induced by Clopidogrel.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of Clopidogrel was associated with increased occult gastrointestinal blood loss. NSAIDs and Clopidogrel should be co-administered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with Clopidogrel should be undertaken with caution.

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when Clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of Clopidogrel was also not significantly influenced by the co-administration of phenobarbital or estrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of Clopidogrel (clopidogrel bisulfate).

At high concentrations in vitro, clopidogrel inhibits P450 (2C9). Accordingly, Clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is co-administered with Clopidogrel.

In addition to the above specific interaction studies, patients entered into clinical trials with

Clopidogrel received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), thrombolytics, heparins (unfractionated and LMWH), GPIIb/IIIa antagonists, antiepileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.

There are no data on the concomitant use of oral anticoagulants, non-study oral anti-platelet drugs and chronic NSAIDs with clopidogrel.

Drug/Laboratory Test Interactions

None known.

4.8 Additional information on special populations

Use in Hepatic-Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel should be used with caution in this population.

Use in Renal-Impaired Patients: Experience is limited in patients with severe renal impairment. Clopidogrel should be used with caution in this population.

4.9 Paediatric population

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

4.10 Fertility, Pregnancy and Lactation:

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, Clopidogrel should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.
	4.11 Effects on ability to drive and use machine: Clopidogrel has no or negligible influence on the ability to drive and use machines.
	4.12 Undesirable Effects: Clopidogrel has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. The following events have been reported spontaneously from worldwide post marketing experience: *Body as a whole:* ▪ hypersensitivity reactions, anaphylactoid reactions, serum sickness *Central and Peripheral Nervous System disorders:* ▪ confusion, hallucinations, taste disorders *Hepato-biliary disorders:* ▪ abnormal liver function test, hepatitis (non-infectious), acute liver failure *Platelet, Bleeding and Clotting disorders:* ▪ cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage) ▪ thrombotic thrombocytopenic purpura (TTP) – some cases with fatal outcome agranulocytosis, aplastic anemia/pancytopenia ▪ conjunctival, ocular and retinal bleeding *Respiratory, thoracic and mediastinal disorders:* ▪ bronchospasm, interstitial pneumonitis *Skin and subcutaneous tissue disorders:* ▪ angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus *Renal and urinary disorders:* ▪ glomerulopathy, increased creatinine levels *Vascular disorders:* ▪ vasculitis, hypotension *Gastrointestinal disorders:* ▪ colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis *Musculoskeletal, connective tissue and bone disorders:* ▪ myalgia
	4.13 Overdose: Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent 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 (in baboons), prostration, difficult breathing, and gastrointestinal

	hemorrhage in all species. Recommendations about specific treatment: Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of Clopidogrel if quick reversal is required.
5.	**Pharmacological properties**
	5.1 Pharmacodynamic Properties: Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting platelet function can reduce the event rate. 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 adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/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. Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other drugs, not all patients will have adequate platelet inhibition. 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.
	5.2 Pharmacokinetics 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. Effect of Food: The effect of food on the bioavailability of the parent compound or active metabolite is currently not known.

	Distribution: Clopidogrel and the main circulating inactive metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable in vitro up to a concentration of 100 mcg/mL. Metabolism: Clopidogrel is extensively metabolized by the liver. In vitro and in vivo, clopidogrel is metabolized 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. 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. In vitro, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. 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-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 elimination half-life of the inactive acid metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Polyethylene Glycol 6000 Isopropyl Alcohol Microcrystalline Cellulose Low-substituted Hydroxy Propyl Cellulose Mannitol Hydrophobic Colloidal Silica Sodium Stearyl Fumarate Wincoat WT-1274 Methylene Chloride
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 36 months from the date of manufacture
	6.4 Special Precautions for storage: Do not store above 30° C. Protect from light and moisture
	6.5 Nature and contents of container: A carton containing 3 strips of 10 tablets along with the pack insert.
	6.6 Special precautions for disposal and other handling : Not applicable

7.	**Marketing authorization holder and manufacturing site addresses:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India Manufacturing site address: Plot no. B-4/5/6, MIDC area Paithan, Aurangabad – 431148. India.
8.	**Marketing authorization number : -**
9.	**Date of first registration/ renewal of the registration:** Aug 01 ,2023
10.	**Date of revision of text: -**