Summary of Product Characteristics
(Product Data Sheet)

1.	**Name of the Medical Product**
	Instaclop Plus **(Clopidogrel 75 mg and Aspirin 75 mg Capsules)**
	1.1 Strength : Clopidogrel Bisulfate USP equivalent to Clopidogrel 75 mg and Aspirin BP 75 mg.
	1.2 Pharmaceutical Dosage Form : Hard gelatin capsules
2.	**Qualitative & Quantitative Composition** Each hard gelatin capsule contains: A) Clopidogrel Bisulfate USP Equivalent to Clopidogrel 75 mg (As two film coated tablets) Each film coated tablet contains: Clopidogrel Bisulfate USP Equivalent to Clopidogrel 37.5 mg Color: Red Oxide of Iron and Titanium Dioxide B) Aspirin BP 75 mg (As enteric coated tablet) Each enteric coated tablet contains: Aspirin BP 75 mg Colour: Titanium Dioxide & Yellow Oxide of Iron Approved colour used in hard gelatin capsule shell
3.	**Pharmaceutical Form:** Pink transparent / Clear transparent, hard gelatin capsule of size "0" containing two pink coloured, circular, biconvex, film coated tablets of Clopidogrel, plain on both sides and one white coloured, circular, biconvex, enteric coated tablet of Asprin, plain on both sides.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Instaclop plus capsules is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). Instaclop plus capsules is a fixed-dose combination medicinal product for continuation of therapy in: • 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 medically treated patients eligible for thrombolytic therapy.

	4.2 Posology and Method of administration: Instaclop Plus capsules should be given as a single daily 75 mg/75 mg dose. Instaclop Plus capsules fixed-dose combination is used following initiation of therapy with Clopidogrel and ASA given separately, and replaces the individual Clopidogrel and ASA products. – In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): 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. If the use of Instaclop Plus capsules is discontinued, patients may benefit with continuation of one antiplatelet medicinal product. – In patients with ST segment elevation acute myocardial infarction: 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. If the use of Instaclop Plus capsules is discontinued, patients may benefit with continuation of one antiplatelet medicinal product. **If a dose is missed:** - Within less than 12 hours after regular scheduled time: patients 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. **Pediatrics population** The safety and efficacy of Instaclop Plus capsules in children and adolescents under 18 years old have not been established. Instaclop Plus capsules is not recommended in this population. **Renal impairment** Instaclop Plus capsules must not be used in patients with severe renal impairment. Therapeutic experience is limited in patients with mild to moderate renal impairment. Therefore Instaclop Plus capsules should be used with caution in these patients. **Hepatic impairment** Instaclop Plus capsules must not be used in patients with severe hepatic impairment. Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore Instaclop Plus capsules should be used with caution in these patients.
	4.3 Method of administration: For oral use. It may be given with or without food.

	4.4 Contraindications: - Hypersensitivity to the drug substance or any component of the product. - Active pathological bleeding such as peptic ulcer or intracranial hemorrhage. - Hypoprothrombinaemia, haemophilia and other bleeding disorders. - Active peptic ulceration or a history of peptic ulceration. - Gout - Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).
	4.5 Special warning and precautions for use: **<u>Clopidogrel:</u>** **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, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. **General Precautions:** - 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: In CAPRIE, Clopidogrel was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (Clopidogrel + aspirin vs. placebo + aspirin, respectively). 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 Hepatically 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 Renally-impaired Patients: Experience is limited in patients with severe renal impairment. Clopidogrel should be used with caution in this population.

	<u>Aspirin:</u> - Caution should be exercised in patients with allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration. - Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects. - The elderly may be more susceptible to the toxic effects of salicylates. Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding. - Caution should be taken in patients with glucose-6-phosphate dehydrogenase deficiency as haemolytic anaemia may occur. - Aspirin may interfere with insulin and glucagon in diabetes. - Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation and therefore it should be discontinued several days before scheduled surgical procedures. Haematological & haemorrhagic effects can occur, and may be severe. Patients should report any unusual bleeding symptoms to their physician. - There is a possible association between aspirin and Reye's Syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease). - Salicylates should not be used in patients with a history of coagulation abnormalities as they may also induce gastro-intestinal haemorrhage, occasionally major. - Aspirin should not be taken by patients with a stomach ulcer or a history of stomach ulcers. - Before commencing long term aspirin therapy for the management of cardiovascular or cerebrovascular disease patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.
	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 : **<u>Clopidogrel</u>** Study of specific drug interactions yielded the following results: - 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. Coadministration 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 coadministered 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 coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of Clopidogrel was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen. The pharmacokinetics of digoxin or theophylline were not modified by the coadministration 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 coadministered 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.

Aspirin:

- Anticoagulants: Aspirin may potentiate the effect of heparin and increases the risk of bleeding with oral anticoagulants, antiplatelet agents and fibrinolytics. Concomitant use is not recommended.
- Other non-steroidal anti-inflammatory drugs (NSAIDs): Concurrent administration can increase side effects. Use of two or more NSAIDs increases risk of gastrointestinal haemorrhage. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.
- Corticosteroids: The risk of gastrointestinal bleeding and ulceration is increased.

	Corticosteroids reduce the plasma salicylate concentration and salicylate toxicity may occur following withdrawal of corticosteroids. - Carbonic anhydrase inhibitors: Reduced excretion of acetazolamide; salicylate intoxication has occurred in patients on high dose salicylate regimes and carbonic anhydrase inhibitors. Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity. - Antacids and adsorbents: The excretion of aspirin is increased in alkaline urine; kaolin possibly reduces absorption. Patients should be advised against ingesting antacids simultaneously to avoid premature drug release. - Mifepristone: The manufacturer of mifepristone recommends that aspirin should be avoided until eight to twelve days after mifepristone has been discontinued. - Antimetabolites: The activity of methotrexate may be markedly enhanced and its toxicity increased. - Antibacterials: The toxicity of sulfonamides may be increased. Alcohol: Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol. - Antiemetics: Metoclopramide enhances the effects of aspirin by increasing the rate of absorption. ACE inhibitors: Aspirin may reduce the antihypertensive effect of ACE inhibitors. - Anti-epileptics: May enhance the effects of phenytoin and sodium valproate. - Diuretics: Antagonism of the diuretic effect of spironolactone. - Hypoglycaemic agents: Aspirin may enhance the effects of insulin and oral hypoglycaemic agents. - Leukotriene antagonists: The plasma concentration of zafirlukst is increased. - Uricosurics: Effect of probenecid and sulfinpyrazone may be reduced. - Thyroid function tests: Aspirin may interfere with thyroid function tests.
	4.8 Additional information on special populations **Pediatrics population** The safety and efficacy of Instaclop Plus capsules in children and adolescents under 18 years old have not been established. Instaclop Plus capsules is not recommended in this population. **Renal impairment** Instaclop Plus capsules must not be used in patients with severe renal impairment. Therapeutic experience is limited in patients with mild to moderate renal impairment. Therefore Instaclop Plus capsules should be used with caution in these patients. **Hepatic impairment** Instaclop Plus capsules must not be used in patients with severe hepatic impairment. Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore Instaclop Plus capsules should be used with caution in these patients.

	4.9 Paediatric population Safety and effectiveness in the pediatric population have not been established.
	4.10 Fertility, Pregnancy and Lactation: **Pregnancy** There are 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. Caution should be exercised when considering use in pregnant patients. Maternal use of aspirin prior to birth may increase the risk of intracranial haemorrhage in premature or low birth weight infants and may contribute to maternal and neonatal bleeding. **Nursing Mothers** 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. As aspirin is excreted in breast milk, Aspirin should not be taken by patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant. High maternal doses may impair platelet function in the infant. **Pediatric Use** Safety and effectiveness in the pediatric population have not been established.
	4.11 Effects on ability to drive and use machine: Data not available for Instaclop Plus capsule.
	4.12 Undesirable Effects: **<u>Clopidogrel</u>:** Hemorrhagic events: - In CAPRIE patients receiving Clopidogrel, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for Clopidogrel compared to 0.5% for aspirin. - In CURE, Clopidogrel use with aspirin was associated with an increase in bleeding compared to placebo with aspirin. There was an excess in major bleeding in patients receiving Clopidogrel plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups. **Adverse Events Occurring in ≥2.5% of Patients using Clopidogrel in CAPRIE trial:** - Body as a Whole – general disorders: Chest pain, Accidental/inflicted injury, Influenza like symptoms, Pain and fatigue - Cardiovascular disorders, general – Oedema, Hypertension - Central and peripheral nervous system disorders - Headache, Dizziness

- GIT disorders - Abdominal pain, Diarrhea, Dyspepsia, Nausea
- Metabolic and nutritional - Hypercholesterolemia
- Musculoskeletal system disorder - Athralgia, back pain
- Platelets/bleeding and clotting disordrs - Bruise/purpura, Epistaxis
- Psychiatric disorders - Depression
- Respiratory system disorders - Upper respiratory tract infection, Dysponea, Rhinitis, Bronchitis, Coughing
- Dermatological - Rash/pruritus
- Urinary system disorders - Urinary tract infection

Aspirin:

Side effects are generally mild and infrequent:

- Blood and the lymphatic system disorders:Aspirin prolongs bleeding time, decreases platelet adhesiveness and, in large doses, may cause hypoprothrombinaemia. Thrombocytopenia may also occur. Bleeding disorders such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, gastrointestinal bleeding, haematoma and cerebral haemorrhage have occasionally been reported. Fatalities have occurred. Haemolytic anaemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Immune system disorder: Hypersensitivity reactions include skin rashes, urticaria, angioedema, asthma, bronchospasm, rhinitis and rarely, anaphylaxis.
- Ear & Labyrinth disorder: Tinnitus.
- Gastrointestinal disorders: Gastrointestinal irritation is common in patients taking aspirin preparations, and nausea, vomiting dyspepsia, gastritis, gastrointestinal erosions and ulceration have been reported. Anaemia may occur following chronic gastrointestinal blood loss or acute haemorrhage.
- Skin and subcutaneous tissue disorders: Skin reactions may occur in susceptible patients.
- Renal and Urinary disorders: urate kidney stones

4.13 Overdose:

Clopidogrel

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.

Aspirin

Salicylate poisoning is usually associated with plasma concentrations >350mg/L (2.5mmol/L) Most adult deaths occur in patients whose concentrations exceed 700mg/L (5.1mmol/L). Single

	doses less than 100mg/kg are unlikely to cause serious poisoning. **Symptoms:** Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases. A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults or children over the age of four years. In children four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier. <u>Uncommon features</u> include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children. **Management:** Give activated charcoal if an adult presents within one hour of ingestion of more than 250mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700mg/L (5.1mmol/L) or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.
5.	**Pharmacological properties**
	5.1 Pharmacodynamic Properties: **<u>Clopidogrel</u>:** **Mechanism of Action** Clopidogrel 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 them can reduce the event rate. Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated.

Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.
Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.
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.

Aspirin:
Aspirin has analgesic, anti-inflammatory and anti-pyretic activity. It also has an antithrombotic action, mediated through inhibition of platelet activation, which has been shown to be useful in secondary prophylaxis following myocardial infarction and in patients with unstable angina or ischaemic stroke including cerebral transient attacks.
In the body it is rapidly converted to the salicylate form which has similar activity and works via the inhibition of the enzyme cyclo-oxygenase, inhibiting prostaglandin synthesis.
The enteric coat is intended to resist gastric fluid whilst allowing disintegration in the intestinal fluid. Owing to the delay that the coating imposes on the release of the active ingredient, enteric coated tablets are unsuitable for the short-term relief of pain.
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30min after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetics Properties:
Clopidogrel:
After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma. Following an oral dose of 14C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating 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.
Effect of Food: Administration of Clopidogrel (clopidogrel bisulfate) with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (≅3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.
Clopidogrel and the main circulating 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 µg/mL.
Metabolism and Elimination: In vitro and in vivo, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Aspirin:
Absorption: Aspirin is rapidly absorbed after oral administration, with some hydrolysis to salicylate before absorption. Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks. Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates and antacids.
Blood concentration: Single and multiple 100 mg doses of enteric- coated aspirin give systemic bioavailabilities of between 15% and 20% of that seen with immediate release aspirin preparations. Cmax of aspirin for several enteric - coated preparations has been shown to be approximately 100 - 200 ng/ml with a half - life of approximately 1.7 hours. Plasma concentrations of salicylic acid increase disproportionately with dose - a 325 mg dose having a half-life of 2-3 hours and higher doses showing lower plasma concentrations in the presence of an increased half-life due to a disproportionate increase in volume of distribution.
Distribution: Aspirin is found in the saliva, milk, plasma and synovial fluid at concentrations less than blood and crosses the placenta. Salicylate - extensive protein binding. Aspirin - protein binding to a small extent.
Metabolism: In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/ glycine conjugation to form glucuronides and salicyluronic acid; oxidation of a small proportion.
Excretion: Excreted in the urine mainly as salicyluronic acid. Salicylate reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of dose excreted as free salicylate.

5.3 Preclinical Safety Data
Carcinogenesis, Mutagenesis, Impairment of Fertility
There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg. Clopidogrel was not genotoxic in four in vitro tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one in vivo test (micronucleus test by oral route in mice). Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m2 basis).

	<u>Aspirin:</u> None applied on the basis of the active ingredient being a well-known and marketed compound with an established efficacy and side effect profile.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Pregelatinized Starch USPNF, Microcrystalline Cellulose USPNF, Glyceryl Distearate BP, Silicon Dioxide USPNF, Yellow oxide of iron IH, Opadry Clear 03K19229 IH, Sodium Stearyl Fumarate BP, Crospovidone BP, Colloidal Silicon Dioxide USPNF, Isopropyl Alcohol BP, Dichloromethane BP, Opadry Enteric 94O580000 White IH, Insta moistshield A21R00941 (Pink) IH, Purified water, Empty Hard Gelatin Capsule Size 0 Transparent pink cap/colourless body.
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 36 months from the date of manufacture
	6.4 Special Precautions for storage: Store below 30°C.
	6.5 Nature and contents of container: 10 capsules in Alu-Alu blister pack, 3 such blisters in a printed carton along with patient information leaflet.
	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 :** Not applicable
9.	**Date of first registration/ renewal of the registration:** Not applicable
10.	**Date of revision of text:** Jul 05, 2018.