

For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

DEPLATT A

1.Generic Name

Clopidogrel and Aspirin Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DEPLATT A 75:

Each film coated bilayered tablet contains:

Clopidogrel Bisulphate I.P.

Equivalent to Clopidogrel 75 mg

Colour: Lack of sunset Yellow

Aspirin I.P. 75 mg

(In coated form)

DEPLATT A 150:

Each film coated bilayered tablet contains:

Clopidogrel Bisulphate I.P.

Equivalent to Clopidogrel 75 mg

Colour: Lack of sunset Yellow

Aspirin I.P. 150 mg

(In coated form)

Excipients used are as below:

HYDROXY PROPYL METHYL CELLULOSE

ETHYL CELLULOSE,

PEG ,

ISO PROPYL ALCOHOL,

METHYLENE CHLORIDE,

LACTOSE ANHYDROUS,

MICROCRYSTALLINE CELLULOSE,

CROSSPOVIDONE

COLLOIDAL SILICON DIOXIDE,

HYDROGENATED CASTOR OIL,

HYDRATED SILICA,

LAKE OF SUNSET YELLOW,

STEARIC ACID,

TALC

SODIUM STARCH GLYCOLATE (DRIED)

CITRIC ACID ANHYDROUS

GLYCERYL BEHANATE

3. DOSAGE FORM AND STRENGTH

DOSAGE FORM: Film Coated Bilayered Tablet

STRENGTH: 75 And 150 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For the treatment of angina, myocardial infraction and stroke.

4.2 Posology and Method of Administration

Dosage: As directed by the Physician.

4.3 Contraindications

Aspirin and Clopidogrel Tablets

- Hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria) active substance and to any of the excipients;
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages;
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia;
- Patients who are suffering from gout;
- Severe renal impairment;
- Severe hepatic impairment
- Doses >100 mg/day during the third trimester of pregnancy
- Methotrexate used at doses >15mg/week

4.4 Special warnings and precautions for use

Clopidogrel

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. 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), or other medicinal products associated with bleeding risk such as pentoxifylline. 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.

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.

CYP2C8 substrates

Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

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. Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopenia and neutropenia. 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.

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.

Aspirin

Aspirin tablets is not suitable for use as an anti-inflammatory/ analgesic/ antipyretic.

Caution should be exercised in patients with allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration, since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects or promote other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid. Aspirin Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Caution should be taken in patients with glucose-6-phosphate dehydrogenase deficiency as haemolytic anaemia may occur

Aspirin tablets is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation and therefore it should be discontinued several days before scheduled surgical procedures. Haematological and haemorrhagic effects can occur, and may be severe. Use with caution before surgery, including tooth extraction. Patients should report any unusual bleeding symptoms to their physician.

Care is advised when stopping antiplatelet therapy after stent insertion either after a fixed period of time or in preparation for a planned surgical procedure, as the balance between stent thrombosis and excessive bleeding has to be carefully assessed.

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).

Aspirin is to be used with caution in cases of hypertension and patients with a stomach ulcer or a history of stomach ulcers or duodenal ulcer or haemorrhagic episodes or undergoing therapy with anticoagulants. Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

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.

Concomitant treatment with Aspirin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox.

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin tablets taken at over dosage.

Aspirin should be avoided in late pregnancy and generally during breast feeding.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs Interaction

Clopidogrel

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. 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.

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.

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.

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

Other concomitant therapy: 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.

Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton Pump Inhibitors (PPI):

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. 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 esomeprazole should be discouraged.

Less pronounced reductions of metabolite exposure have been observed with pantoprazole or lansoprazole. The plasma concentrations of the active metabolite were 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

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 were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption. Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

CYP2C8 substrate medicinal products: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

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.

Aspirin

Contraindicated combinations

Methotrexate (used at doses >15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin tablets is contraindicated.

Not recommended combinations

Uricosuric agents, e.g. probenecid and sulfinpyrazone:

Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants e.g. coumarin, heparin, warfarin and phenindione:

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

Anti-platelet agents (e.g. clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine):

Increased risk of gastrointestinal bleeding.

Antidiabetics, e.g. sulphonylureas:

Salicylics may increase the hypoglycaemic effect of sulphonylureas.

Digoxin and lithium:

Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is

recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensive:

NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. Patients with hypertension should be carefully monitored. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency. Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is 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.

Ibuprofen:

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.

Ciclosporin, tacrolimus:

Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Systemic Corticosteroids:

The risk of gastrointestinal bleeding and ulceration is increased when acetylsalicylic acid and corticosteroids are co-administered. Corticosteroids reduce the plasma salicylate concentration and salicylate toxicity may occur following withdrawal of corticosteroids.

Methotrexate (used at doses <15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

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. Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

Mifepristone:

The manufacturer of mifepristone recommends that aspirin should be avoided until eight to twelve days after mifepristone has been discontinued.

Alcohol:

Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

Antiemetics:

Metoclopramide enhances the effects of aspirin by increasing the rate of absorption.

Anti-epileptics:

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered. Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Leukotriene antagonists:

The plasma concentration of zafirlukast is increased.

Antibacterials:

The toxicity of sulphonamides may be increased.

Thyroid function tests:

Aspirin may interfere with thyroid function tests.

4.6 Use In Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Clopidogrel

Pregnancy

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, parturition or postnatal development.

Breast-feeding

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.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

Aspirin

Pregnancy

Low doses (up to 100 mg/day):

Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100- 500 mg/day:

There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Lactation

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.

4.7 Effects On Ability to Drive and Use Machines

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

4.8 Undesirable Effects

Clopidogrel

Summary of the safety profile

Clopidogrel has been evaluated for safety in more than 44,000 patients who have participated in clinical studies, including over 12,000 patients treated for 1 year or more. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY,

COMMIT and ACTIVE-A studies are discussed below. 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 postmarketing experience where it was mostly reported during the first month of treatment.

In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was similar for clopidogrel and ASA.

In CURE, there was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the placebo plus ASA group. The incidence of major bleeding was similar between groups. This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups.

In ACTIVE-A, the rate of major bleeding was greater in the clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extracranial origin in both groups (5.3% in the clopidogrel + ASA group; 3.5% in the placebo +ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the clopidogrel + ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the clopidogrel + ASA group and 0.7% in the placebo +ASA group) and haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

Tabulated list of adverse reactions

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 ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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.

System Class	Organ	Common	Uncommon	Rare	Very rare, not known*
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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 A, granulocytopenia, anaemia
Cardiac disorders				Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*
Immune system disorders				Serum sickness, anaphylactoid reactions, cross- reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel)*, insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)*
Psychiatric disorders				Hallucinations, confusion

Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances, ageusia
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
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura)		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			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	Bleeding puncture site			Fever

administration site conditions				
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

* Information related to clopidogrel with frequency “not known”.

Aspirin

Side effects are grouped on the basis of System Organ Class. Within each system organ class, the frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	<p><i>Common:</i></p> <p>Increased bleeding tendencies.</p> <p><i>Rare:</i></p> <p>Thrombocytopenia, granulocytosis, aplastic anaemia.</p> <p><i>Not known:</i></p> <p>Cases of bleeding with prolonged bleeding time such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, haematoma, cerebral haemorrhage and gingival bleeding.</p> <p>Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result, there may be an increased risk of bleeding during surgical procedures.</p> <p>Aspirin decreases platelet adhesiveness and, in large doses, may cause hypoprothrombinaemia.</p> <p>Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).</p> <p>Haemolytic anaemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.</p>
Immune system disorders	<p><i>Rare:</i></p> <p>Hypersensitivity reactions, skin rashes, urticarial, asthma, bronchospasm, angio-oedema, allergic oedema, anaphylactic reactions including shock.</p>

Metabolism and digestive system disorders	<i>Not known:</i> Hyperuricemia.
Nervous system disorders	<i>Rare:</i> Intracranial haemorrhage <i>Not known:</i> Headache, vertigo.
Ear and labyrinth disorders	<i>Not known:</i> Reduced hearing ability; tinnitus.
Vascular disorders	<i>Rare:</i> Hemorrhagic vasculitis.
Respiratory, thoracic and mediastinal disorders	<i>Uncommon:</i> Rhinitis, dyspnoea. <i>Rare:</i> Bronchospasm, asthma attacks.
Reproductive system and mammary disorders	<i>Rare:</i> Menorrhagia
Gastrointestinal disorders	<i>Common:</i> Dyspepsia. <i>Rare:</i> Severe gastrointestinal haemorrhage, nausea, vomiting. <i>Not known:</i> Gastric or duodenal ulcers and perforation, diarrhoea.
Hepatobiliary disorders	<i>Not known:</i> Hepatic insufficiency
Skin and subcutaneous tissue disorders	<i>Uncommon:</i> Urticaria. <i>Rare:</i> Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.

Renal and urinary tract disorders	<i>Not known:</i> Impaired renal function, salt and water retention, urate kidney stones.
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4.9 Overdose

Clopidogrel

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.

Aspirin

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/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 aged 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.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, 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.

Treatment

Give activated charcoal if an adult present within one hour of ingestion of more than 250 mg/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 >700 mg/L (5.1 mmol/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 Mechanism of Action

Clopidogrel

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.

Aspirin

Aspirin (acetylsalicylic acid) irreversibly acetylates platelet cyclo-oxygenase thereby inhibiting the biosynthesis of thromboxane, a potent vasoconstrictor and inducer of platelet aggregation. It also inhibits the action of cyclo-oxygenase in the vascular endothelial wall preventing the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation.

5.2 Pharmacodynamic Properties

Clopidogrel

Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC04.

Pharmacodynamic effects

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this 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.

Clinical efficacy and safety

The safety and efficacy of clopidogrel have been evaluated in 5 double-blind studies involving over 88,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, COMMIT and ACTIVE-A studies comparing clopidogrel to placebo, both medicinal products given in combination with ASA and other standard therapy.

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease

The CAPRIE study included 19,185 patients with atherothrombosis as manifested by recent myocardial infarction (<35 days), recent ischaemic stroke (between 7 days and 6 months) or established peripheral arterial disease (PAD). Patients were randomised to clopidogrel 75 mg/day or ASA 325 mg/day, and were followed for 1 to 3 years. In the myocardial infarction subgroup, most of the patients received ASA for the first few days following the acute myocardial infarction.

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; $p=0.045$), which corresponds, for every 1,000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).

In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at $p=0.003$) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR = 7.3%; CI: -5.7 to 18.7 [$p=0.258$]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR = -4.0%; CI: -22.5 to 11.7 [$p=0.639$]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤ 75 years.

Since the CAPRIE trial was not powered to evaluate efficacy of individual subgroups, it is not clear whether the differences in relative risk reduction across qualifying conditions are real, or a result of chance.

Acute coronary syndrome

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, $N=6,259$) or placebo ($N=6,303$), both given in combination with ASA (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel and placebo was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; $p=0.00009$) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12-month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted.

The use of clopidogrel in CURE was associated with a decrease in the need of thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel-treated group and 1,187 (18.8%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, $p=0.0005$) for the clopidogrel-treated group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel treated group and 363 (5.8%) in the placebo treated group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering medicinal products, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily).

In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, $n=1,752$) or placebo ($n=1,739$), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients ≥ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel group and 21.7% in the placebo group reached the primary endpoint, representing an absolute reduction of 6.7% and a 36% odds reduction in favor of clopidogrel (95% CI: 24, 47%; $p < 0.001$), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day, $n=22,961$) or placebo ($n=22,891$), in combination with ASA (162 mg/day), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first

occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients ≥ 60 years (26% ≥ 70 years) and 54.5% patients who received fibrinolytics.

Clopidogrel significantly reduced the relative risk of death from any cause by 7% ($p=0.029$), and the relative risk of the combination of re-infarction, stroke or death by 9% ($p=0.002$), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

De-escalation of P2Y12 Inhibitor Agents in ACS

Switching from a more potent P2Y12 receptor inhibitor to clopidogrel in association with aspirin after acute phase in ACS has been evaluated in two randomized investigator-sponsored studies (ISS) – TOPIC and TROPICAL-ACS – with clinical outcome data.

The clinical benefit provided by the more potent P2Y12 inhibitors, ticagrelor and prasugrel, in their pivotal studies is related to a significant reduction in recurrent ischaemic events (including acute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischaemic benefit was consistent throughout the first year, greater reduction in ischaemic recurrence after ACS was observed during the initial days following the treatment initiation. In contrast, post-hoc analyses demonstrated statistically significant increases in the bleeding risk with the more potent P2Y12 inhibitors, occurring predominantly during the maintenance phase, after the first month post-ACS. TOPIC and TROPICAL-ACS were designed to study how to mitigate the bleeding events while maintaining efficacy.

TOPIC (*Timing of Platelet Inhibition after acute Coronary syndrome*)

This randomized, open-label trial included ACS patients requiring PCI. Patients on aspirin and a more potent P2Y12 blocker and without adverse event at one month were assigned to switch to fixed-dose aspirin plus clopidogrel (de-escalated dual antiplatelet therapy (DAPT)) or continuation of their drug regimen (unchanged DAPT).

Overall, 645 of 646 patients with STEMI or NSTEMI or unstable angina were analyzed (de-escalated DAPT ($n=322$); unchanged DAPT ($n=323$)). Follow-up at one year was performed for 316 patients (98.1%) in the de-escalated DAPT group and 318 patients (98.5%) in the unchanged DAPT group. The median follow-up for both groups was 359 days. The characteristics of the studied cohort were similar in the 2 groups.

The primary outcome, a composite of cardiovascular death, stroke, urgent revascularization, and BARC (Bleeding Academic Research Consortium) bleeding ≥ 2 at 1-year post ACS, occurred in 43 patients (13.4%) in the de-escalated DAPT group and in 85 patients (26.3%) in the unchanged DAPT group ($p<0.01$). This statistically significant difference was mainly driven by fewer bleeding events, with no difference reported in ischaemic endpoints ($p=0.36$), while BARC ≥ 2 bleeding occurred less frequently in the de-escalated DAPT group (4.0%) versus 14.9% in the unchanged DAPT group ($p<0.01$). Bleeding events defined as all BARC occurred in 30 patients (9.3%) in the de-escalated DAPT group and in 76 patients (23.5%) in the unchanged DAPT group ($p<0.01$).

TROPICAL-ACS (*Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes*)

This randomized, open-label trial included 2,610 biomarker-positive ACS patients after successful PCI. Patients were randomized to receive either prasugrel 5 or 10 mg/d (Days 0-14) ($n=1309$), or prasugrel 5 or 10 mg/d (Days 0-7) then de-escalated to clopidogrel 75 mg/d (Days

8-14) (n=1309), in combination with ASA (<100 mg/day). At Day 14, platelet function testing (PFT) was performed. The prasugrel-only patients were continued on prasugrel for 11.5 months.

The de-escalated patients underwent high platelet reactivity (HPR) testing. If $HPR \geq 46$ units, the patients were escalated back to prasugrel 5 or 10 mg/d for 11.5 months; if $HPR < 46$ units, the patients continued on clopidogrel 75 mg/d for 11.5 months. Therefore, the guided de-escalation arm had patients on either prasugrel (40%) or clopidogrel (60%). All patients were continued on aspirin and were followed for one year.

The primary endpoint (the combined incidence of CV death, MI, stroke and BARC bleeding grade ≥ 2 at 12 months) was met showing non-inferiority. Ninety-five patients (7%) in the guided de-escalation group and 118 patients (9%) in the control group (p non-inferiority=0.0004) had an event. The guided de-escalation did not result in an increased combined risk of ischemic events (2.5% in the de-escalation group vs 3.2% in the control group; p non-inferiority=0.0115), nor in the key secondary endpoint of BARC bleeding ≥ 2 (5% in the de-escalation group versus 6% in the control group ($p=0.23$)). The cumulative incidence of all bleeding events (BARC class 1 to 5) was 9% (114 events) in the guided de-escalation group versus 11% (137 events) in the control group ($p=0.14$)

Atrial fibrillation

The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrollment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

The ACTIVE-W study demonstrated that anticoagulant treatment with vitamin K antagonists was more effective than with clopidogrel and ASA.

The ACTIVE-A study (N=7,554) was a multicenter, randomized, double-blind, placebocontrolled study which compared clopidogrel 75 mg/day + ASA (N=3,772) to placebo + ASA (N=3,782). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and had at least one of the following risk factors: age ≥ 75 years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction $< 45\%$; or documented peripheral vascular disease. The mean CHADS2 score was 2.0 (range 0-6).

The major exclusion criteria for patients were documented peptic ulcer disease within the previous 6 months; prior intracerebral hemorrhage; significant thrombocytopenia (platelet count $< 50 \times 10^9/l$); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance to any of the two compounds.

Seventy-three percent (73%) of patients enrolled into the ACTIVE-A study were unable to take VKA due to physician assessment, inability to comply with INR (international normalised ratio) monitoring, predisposition to falling or head trauma, or specific risk of bleeding; for 26% of the patients, the physician's decision was based on the patient's unwillingness to take VKA. The patient population included 41.8 % women. The mean age was 71 years, 41.6% of patients were

≥75 years. A total of 23.0% of patients received anti-arrhythmics, 52.1% beta-blockers, 54.6% ACE inhibitors, and 25.4% statins.

The number of patients who reached the primary endpoint (time to first occurrence of stroke, MI, non-CNS systemic embolism or vascular death) was 832 (22.1%) in the group treated with clopidogrel + ASA and 924 (24.4%) in the placebo + ASA group (relative risk reduction of 11.1%; 95% CI of 2.4% to 19.1%; p=0.013), primarily due to a large reduction in the incidence of strokes. Strokes occurred in 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receiving placebo + ASA (relative risk reduction, 28.4%; 95% CI, 16.8% to 38.3%; p=0.00001).

Paediatric population

In a dose escalation study of 86 neonates or infants up to 24 months of age at risk for thrombosis (PICOLO), clopidogrel was evaluated at consecutive doses of 0.01, 0.1 and 0.2 mg/kg in neonates and infants and 0.15 mg/kg only in neonates. The dose of 0.2 mg/kg achieved the mean percent inhibition of 49.3% (5 µM ADP-induced platelet aggregation) which was comparable to that of adults taking Clopidogrel 75 mg/day.

In a randomised, double-blind, parallel-group study (CLARINET), 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-topulmonary arterial shunt were randomised to receive clopidogrel 0.2 mg/kg (n=467) or placebo (n=439) along with concomitant background therapy up to the time of second stage surgery. The mean time between shunt palliation and first administration of study medicinal product was 20 days. Approximately 88% of patients received concomitant ASA (range of 1 to 23 mg/kg/day). There was no significant difference between groups in the primary composite endpoint of death, shunt thrombosis or cardiac-related intervention prior to 120 days of age following an event considered of thrombotic nature (89 [19.1%] for the clopidogrel group and 90 [20.5%] for the placebo group). Bleeding was the most frequently reported adverse reaction in both clopidogrel and placebo groups; however, there was no significant difference in the bleeding rate between groups. In the long-term safety follow-up of this study, 26 patients with the shunt still in place at one year of age received clopidogrel up to 18 months of age. No new safety concerns were noted during this long-term follow-up.

The CLARINET and the PICOLO trials were conducted using a constituted solution of clopidogrel. In a relative bioavailability study in adults, the constituted solution of clopidogrel showed a similar extent and slightly higher rate of absorption of the main circulating (inactive) metabolite compared to the authorised tablet.

Aspirin

Pharmacotherapeutic group: Platelet Aggregation Inhibitor Excl. Heparin, ATC code: B01AC06

The antiplatelet effect of aspirin is largely unrelated to its systemic bioavailability and its duration of effect does not correlate with the presence of intact salicylic acid in the circulation. The antiplatelet effect is considered to be largely pre-systemic, associated with acetylation of platelet cyclo-oxygenase in the portal circulation.

However, as the endothelial cell is capable of synthesising new cyclo-oxygenase, whereas the platelet is not, the effect on thromboxane is longer lasting.

Due to the low dose enteric-coated formulation of Aspirin 75mg Gastro-Resistant Tablets acetylsalicylic acid is slowly released into the portal circulation and is deacetylated by the liver to inactive salicylate before reaching the systemic circulation. It is postulated that platelets

passing through the portal circulation are exposed to acetylsalicylic acid concentrations sufficient to achieve effective thromboxane inhibition, while systemic prostacyclin synthesis remains essentially unaffected.

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 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin 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.

5.3 Pharmacokinetic Properties

Clopidogrel

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 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-oxoclopidogrel 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 C_{max} 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. C_{max} occurs approximately 30 to 60 minutes after dosing.

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.

Pharmacogenetics

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.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metaboliser genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μ M ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 μ M ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1477), and ACTIVE-A (n=601), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

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 subjects 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 subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects 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 subjects. The mean bleeding time prolongation was also similar in the two groups.

Race

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity. From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

Aspirin

Aspirin is rapidly absorbed after oral administration of conventional release preparations, 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. Plasma concentrations of the drug increase disproportionately to the dose; e.g. 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 the volume of distribution.

Aspirin is found in saliva, milk, plasma and synovial fluid at concentrations less than in blood and crosses the placenta. Salicylate/protein binding extensive. Aspirin/protein binding to a small extent. In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/glycine conjugation to form glucuronides and 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.

The absolute bioavailability of aspirin from Aspirin 75mg Gastro-Resistant Tablets (compared with intravenous aspirin solution) is approximately 25%.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Clopidogrel

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic

metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies, and showed no genotoxic activity.

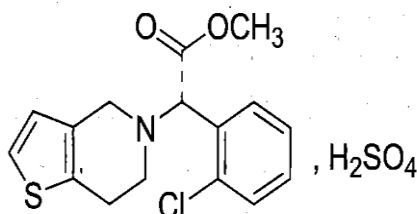
Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

Aspirin

There are no pre-clinical data of relevance.

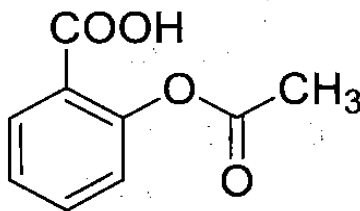
7. DESCRIPTION

- The chemical name of Clopidogrel Bisulphate is methyl (S)- α -(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5-(4H) acetate sulphate (IUPAC). Its molecular formula is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9. The chemical structure is:



Clopidogrel Bisulphate is a white to off-white powder.

- The chemical name of Aspirin is 2-aceoxybenzoic acid (IUPAC). Its molecular formula is $C_9H_8O_4$ and its molecular weight is 180.2. The chemical structure is:



- Aspirin is Colourless crystal or White, Crystalline Powder, odourless or almost odourless.
- Product Description:
- DEPLATT A 75:
- Bilayered film coated flat tablets with light orange coloured layer having dark orange spots on one side and white coloured layer having white shiny spots on other side of tablets.
- DEPLATT A 150:
- Bilayered film coated flat tablets with white coloured layer having white shiny spots on one side and light orange coloured layer having dark orange spots and bisecting line on other side of tablets.
-

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

To be provided by RA TEAM

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

DEPLATT A is Available in blister pack of 15 tablets..

8.4 Storage and Handing Instructions

Store below 25°C, in dry place. Keep all tablets out of the reach of children.

9. PATIENT COUNSELLING INFORMATION

Clopidogrel

Package leaflet: Information for the user

clopidogrel/ Aspirin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

- If you have any side effects, including any side effects not listed in this leaflet, talk to your doctor or pharmacist.

What is in this leaflet

1. What DEPLATT A is and what it is used for
2. What you need to know before you take DEPLATT A
3. How to take DEPLATT A
4. Possible side effects
5. How to store DEPLATT A
6. Contents of the pack and other information

1. What DEPLATT A is and what it is used for

DEPLATT A contains clopidogrel and acetylsalicylic acid (ASA) and belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping in some types of blood vessels (called arteries), antiplatelet medicinal products reduce the chances of blood clots forming (a process called atherothrombosis).

DEPLATT A is taken by adults to prevent blood clots forming in hardened arteries which can lead to atherothrombotic events (such as stroke, heart attack, or death). You have been prescribed Clopidogrel/Aspirin in place of the two separate medicines, clopidogrel and Aspirin, to help prevent blood clots because you have experienced a severe type of chest pain known as 'unstable angina' or heart attack (myocardial infarction).

2. What you need to know before you take Clopidogrel

Do not take DEPLATT A

- if you are allergic to clopidogrel, acetylsalicylic acid (ASA) or any of the other ingredients of this medicine.
- if you are allergic to other products called non-steroidal anti-inflammatory products usually used to treat painful and/or inflammatory conditions of muscles or joints.
- if you have a medical condition that includes the combination of asthma, nasal discharge (runny nose) and polyps (a type of growth in the nose).
- if you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain.
- if you suffer from severe liver disease.
- if you suffer from severe kidney disease.
- if you are in your last trimester of pregnancy.

Warnings and precautions

If any of the situations mentioned below apply to you, you should tell your doctor before taking Clopidogrel/Aspirin:

- if you have a risk of bleeding such as:

- a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer).
- a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body).
- a recent serious injury.
- a recent surgery (including dental).
- a planned surgery (including dental) in the next seven days.
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred in the last seven days.
- if you have kidney or liver disease.
- if you have a history of asthma or allergic reactions including allergy to any medicine used to treat your disease.
- if you have gout.
- if you drink alcohol, because of the increased risk of bleeding or gastrointestinal injury.
- if you have a condition known as glucose-6-phosphate dehydrogenase (G6PD) deficiency because of the risk of a particular form of anaemia (low number of red blood cells). While you are taking Clopidogrel/Aspirin:
 - You should tell your doctor
 - if a surgery (including dental) is planned.
 - if you have any stomach or abdominal pain or bleeding in the stomach or bowels (red stools or black stools).
 - You should also tell your doctor immediately if you develop a medical condition known as Thrombotic Thrombocytopenic Purpura or TTP that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice).
 - If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway
 - Your doctor may order blood tests.

Children and adolescents

Clopidogrel/Aspirin is not intended for use in children or adolescents less than 18 years of age. There is a possible association between acetylsalicylic acid (ASA) and Reye's Syndrome when products containing ASA are given to children or adolescents with a viral infection. Reye's Syndrome is a very rare disease which can be fatal.

Other medicines and Clopidogrel/Aspirin

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Some other medicines may influence the use of Clopidogrel/Aspirin or vice versa.

You should specifically tell your doctor if you take

- medicines that may increase your risk of bleeding such as:
 - oral anticoagulants, medicines used to reduce blood clotting,
 - ASA or another non-steroidal anti-inflammatory medicine usually used to treat painful and/or inflammatory conditions of muscle or joints,
 - heparin or any other injectable medicine used to reduce blood clotting,
 - ticlopidine, other antiplatelet agent, - a selective serotonin reuptake inhibitor (including but not restricted to fluoxetine or fluvoxamine), medicines usually used to treat depression,
- omeprazole or esomeprazole, medicines to treat upset stomach,
- methotrexate, a medicine used to treat severe joint disease (rheumatoid arthritis) or skin disease (psoriasis),
- acetazolamide, a medicine used to treat glaucoma (increased ocular pressure) or epilepsy or to increase urine flow,
- probenecid, benzbromarone, or sulfapyrazone, medicines used to treat gout,
- fluconazole or voriconazole, medicines to treat fungal infections,
- efavirenz or tenofovir, medicines to treat HIV (human immunodeficiency virus) infections,
- valproic acid, valproate or carbamazepine, medicines to treat some forms of epilepsy,
- the varicella vaccine, a medicine used to prevent chickenpox or shingles, within 6 weeks of taking Clopidogrel/Aspirin, or if you have active chickenpox or shingles infection (see section 2 'Children and adolescents'),
- moclobemide, medicine to treat depression,
- repaglinide, medicine to treat diabetes,
- paclitaxel, medicine to treat cancer,
- nicorandil, medicine to treat cardiac chest pain.

You should stop other clopidogrel treatment while you are taking Clopidogrel/Aspirin. An occasional use of ASA (no more than 1,000 mg in any 24-hour period) should generally not cause a problem, but prolonged use of ASA in other circumstances should be discussed with your doctor or pharmacist.

Pregnancy and breast-feeding

Do not take Clopidogrel/Aspirin during third trimester of pregnancy. It is preferable not to take this medicine during first and second trimesters of pregnancy.

If you are pregnant or suspect that you are pregnant, you should tell your doctor or your pharmacist before taking Clopidogrel/Aspirin. If you become pregnant while taking Clopidogrel/Aspirin, consult your doctor immediately as it is recommended not to take Clopidogrel/Aspirin while you are pregnant.

You should not breast-feed while using this medicine.

If you are breast-feeding or planning to breast-feed, talk to your doctor before taking this medicine. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Clopidogrel/Aspirin should not affect your ability to drive or to use machines. This may cause stomach upset or diarrhoea.

3. How to take DEPLATT A

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet of Clopidogrel/Aspirin per day to be taken orally with a glass of water,

You should take your medicine at the same time each day. Depending on your condition, your doctor will determine the length of time for which you need to take Clopidogrel/Aspirin.

If you have had a heart attack, it should be prescribed for at least four weeks. In any case, you should take it for as long as your doctor continues to prescribe it.

If you take more DEPLATT A

Contact your doctor or the nearest hospital emergency department because of the increased risk of bleeding. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you forget to take DEPLATT A

If you miss a dose, wait until it is time for your next dose, then go on as normal. Do not take a double dose to make up for a forgotten tablet. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you stop taking Clopidogrel/Aspirin

Do not stop the treatment unless your doctor tells you so. Contact your doctor before stopping or restarting your treatment. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:

- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells.
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots, and/or confusion.
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

Reddening of the skin with blisters or peeling and may be associated with a high fever and joint pains. This could be erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome.

- Unusual bleeding, such as coughing up blood, blood in your vomit or urine, or black stools.

The most common side effect which has been seen with Clopidogrel/Aspirin is bleeding. Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head (especially in elderly), the lung or the joints has also been reported.

If you experience prolonged bleeding when taking Clopidogrel/Aspirin If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries

e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway.

Other side effects include:

Common side effects (may affect up to 1 in 10 people):

Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (may affect up to 1 in 100 people):

Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, sensation of tingling and numbness. • Hives. • Runny noses. • Breathing difficulty.

Rare side effect (may affect up to 1 in 1000 people):

Vertigo, enlarged breasts in males. Severe bleeding in the stomach or intestines, brain haemorrhage; altered number of

blood cells.

- Nausea and vomiting.
- Cramps in the lower respiratory tract, asthma attack.
- Inflammation in the blood vessels.
- Bruising with purple spots (cutaneous bleeding).
- Severe skin reactions such as rash known as erythema multiforme and its life threatening forms Stevens-Johnson syndrome and Lyell's syndrome.
- Hypersensitivity reactions, such as swelling of e.g. lips, face or body, or shock.
- Abnormal heavy or prolonged menstrual periods

Very rare side effects (may affect up to 1 in 10,000 people):

Jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions (for example, overall sensation of heat with sudden general discomfort until fainting); swelling in the mouth; blisters of the skin; skin allergy; sore mouth

(stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in taste or loss of taste of food.

Side effects with frequency not known (frequency cannot be estimated from the available data):

Hypersensitivity reactions with chest or abdominal pain, persistent low blood sugar symptoms.

In addition, your doctor may identify changes in your blood or urine test results.

- Ringing in your ears (tinnitus) or reduced hearing ability.
- Headache.
- Vertigo.
- Ulcers in stomach or small intestine and perforation.

- Prolonged bleeding time.
- Impaired kidney function.
- Salt or water retention which may cause swelling of hands, feet, legs, stomach, breasts or face.
- Impaired liver function.
- High level of uric acid in the blood.

5. How to store DEPLATT A

Store below 25°C, in dry place. Keep all tablets out of the reach of children.

6 Contents of the pack and other information

What DEPLATT A

The active substances are clopidogrel and Aspirin. Each tablet contains 75 mg of clopidogrel, 75 mg of Aspirin. And 150 mg of Aspirin.

The other ingredients are:

HYDROXY PROPYL METHYL CELLULOSE

ETHYL CELLULOSE,

PEG ,

ISO PROPYL ALCOHOL,

METHYLENE CHLORIDE,

LACTOSE ANHYDROUS,

MICROCRYSTALLINE CELLULOSE,

CROSSPOVIDONE

COLLOIDAL SILICON DIOXIDE,

HYDROGENATED CASTOR OIL,

HYDRATED SILICA,

LAKE OF SUNSET YELLOW,

STEARIC ACID,

TALC

SODIUM STARCH GLYCOLATE (DRIED)

CITRIC ACID ANHYDROUS

GLYCERYL BEHANATE

10. DETAILS OF MANUFACTURER

TORRENT PHARMACEUTICALS LTD.

32 No., Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

M/563/2010 issued on 03.09.2013

12. DATE OF REVISION

July 2019

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/DEPLATT A 75,150mg/JUL-19/06/PI

