1.3 Product information

1.3.1 Summary of Product Characteristics (Smpc)

1. NAME OF THE MEDICINAL PRODUCT:

Clopidogrel Tablets USP 75 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film coated tablet contains:
Clopidogrel Bisulfate USP
equivalent to Clopidogrel 75 mg.
Colours: Red Oxide of Iron & Titanium Dioxide BP.

3. PHARMACEUTICAL FORM:

Light brown to brown coloured circular biconvex film coated tablet with plain on both sides.

4. Clinical Particulars:

4.1 Therapeutic Indication:

Secondary prevention of atherothrombotic events
Clopidogrel is indicated in:

• Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

• Adult patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
- ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy. In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)

Clopidogrel in combination with ASA is indicated in:

- Adult patients with moderate to high-risk TIA (ABCD21 score $\geq$4) or minor IS (NIHSS2 $\leq$ 3) within 24 hours of either the TIA or IS event.

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

For further information please refer to section 5.1.
1 Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnosis

4.2 Posology and Method of Administration

Posology

• Adults and elderly

Clopidogrel should be given as a single daily dose of 75 mg.

In patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.

- ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg loading dose in combination with ASA and with or without thrombolytics. For patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting.

Adult patients with moderate to high-risk TIA or minor IS:

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

In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel (see section 5.1).

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.

• Paediatric population

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

• Renal impairment

Therapeutic experience is limited in patients with renal impairment.

• Hepatic impairment

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

Method of administration
For oral use
It may be given with or without food.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.4 Special warnings and precautions for use
Bleeding and haematological disorders
Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section
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 CYP2C19 strong inducers or other medicinal products associated with bleeding risk such as pentoxifylline (see section 4.5). Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.5). 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 ischemic stroke

- Initiation of therapy
  - In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and ASA) should be started no later than 24 hours after the event onset. There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial hemorrhage.
  - In non-minor IS patients, clopidogrel monotherapy should be started only after the first 7 days of the event.
- Non-minor IS patients (NIHSS >4)

In view of the lack of data, use of dual antiplatelet therapy is not recommended .

- Recent minor IS or moderate to high-risk TIA in patients for whom intervention is indicated or planned

There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype. Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2).

Use of medicinal products that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.5).

CYP2C8 substrates Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5).

Cross-reactions among thienopyridines

Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see section 4.8). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological

reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Renal impairment

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients (see section 4.2).

Hepatic impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.2).

Excipients

Aclotil contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution. Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. 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. Coadministration 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 nonfibrin 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 coadministered with caution (see section 4.4).

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:

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel. Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.

Inhibitors of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see sections 4.4 and 5.2). 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 has been observed with pantoprazole or lansoprazole. The plasma concentrations of the active metabolite was 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. Boosted anti-retroviral therapy (ART): HIV patients treated with boosted anti-retroviral therapies (ART) are at high risk of vascular events. A significantly reduced platelet inhibition has been shown in HIV patients treated with ritonavir-or cobicistat-boosted ART. Although the clinical relevance of these findings is uncertain, there have been spontaneous reports of HIV-infected patients treated with ritonavir boosted ART, who have experienced re-occlusive events after de-obstruction or have suffered thrombotic events under a clopidogrel loading treatment schedule. Average platelet inhibition can be decreased with concomitant use of clopidogrel and ritonavir. Therefore, concomitant use of clopidogrel with ART boosted therapies should be discouraged.

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 coadministration 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 (see section 4.4). 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. As with other oral P2Y12 inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3).

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, breastfeeding should not be continued during treatment with Aclotil.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 Post marketing 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 hemorrhagic 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 (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Blood and the Lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including Severeneutropenia	Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), 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				Serum sickness, anaphylactoid

disorders				reactions, crossreactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)*, 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 caseswere 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 hemorrhage, hemorrhage of

				operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary hemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic Pneumonia
Gastrointestinal disorders	Gastrointestinal hemorrhage, diarrhoea,Abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea,constipation, flatulence	Retroperitoneal hemorrhage	Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepatobiliary 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, druginduced

				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 tissueand bone disorders				Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, Myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and Administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

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

4.9 Overdose

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.
No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC-04.
Mechanism of action
Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein 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.
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 7 double-blind studies involving over 100,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY, COMMIT, CHANCE, POINT 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 ischemic 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 ischemic events (combined end point of myocardial infarction, ischemic 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 ischemic 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, ischemic 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 ischemia. Patients were required to have either ECG changes compatible with new ischemia 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 hemorrhage persisted (see section 4.4). 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 ischemia) 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 coprimary endpoint (CV death, MI, stroke or refractory ischemia). 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 infarctrelated 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 Acute Coronary Syndrome

Switching from a more potent P2Y12 receptor inhibitor to clopidogrel in association with aspirin after acute phase in Acute Coronary Syndrome (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 ischemic events (including acute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischemic benefit was consistent throughout the first year, greater reduction in ischemic 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 percutaneous coronary intervention (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 ST-elevation-MI (STEMI) or non-ST-elevation-MI (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 ischemic 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=1306), or prasugrel 5 or 10 mg/d (Days 0-7) then de-escalated to clopidogrel 75 mg/d (Days 8-14) (n=1304), 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≥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 ($p=0.14$).

Dual Antiplatelet Therapy (DAPT) in Acute Minor IS or Moderate to High-risk TIA DAPT with combination clopidogrel and ASA as a treatment to prevent stroke after an acute minor IS or moderate to high-risk TIA has been evaluated in two randomized investigator-sponsored studies (ISS) – CHANCE and POINT – with clinical safety and efficacy outcome data. CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events)

This randomized, double-blinded, multicenter, placebo-controlled clinical trial included 5,170 Chinese patients with acute TIA (ABCD2 score ≥4) or acute minor stroke (NIHSS ≤3).

Patients in both groups received open-label ASA on day 1 (with the dose ranging from 75 to 300 mg, at the discretion of the treating physician). Patients randomly assigned to the clopidogrel–ASA group received a loading dose of 300 mg of clopidogrel on day 1, followed by a dose of 75 mg of clopidogrel per day on days 2 through 90, and ASA at a dose of 75 mg per day on days 2 through 21. Patients randomly assigned to the ASA group received a placebo version of clopidogrel on days 1 through 90 and ASA at a dose of 75 mg per day on days 2 through 90.

The primary efficacy outcome was any new stroke event (ischemic and hemorrhagic) in the first 90 days after acute minor IS or high-risk TIA. This occurred in 212 patients (8.2%) in the clopidogrel-ASA group compared with 303 patients (11.7%) in the ASA group (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.57 to 0.81; P<0.001). IS occurred in 204 patients (7.9%) in the clopidogrel–ASA group compared with 295 (11.4%) in the ASA group (HR, 0.67; 95% CI, 0.56 to 0.81; P<0.001). Hemorrhagic stroke occurred in 8 patients in each of the two study groups (0.3% of each group). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel– ASA group and in eight (0.3%) in the ASA group (P = 0.73). The rate of any bleeding event was 2.3% in the clopidogrel–ASA group as compared with 1.6% in the ASA group (HR, 1.41; 95% CI, 0.95 to 2.10; P = 0.09).

POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)

This randomized, double-blinded, multicenter, placebo-controlled clinical trial included 4,881 international patients with acute TIA (ABCD2 score ≥4) or minor stroke (NIHSS ≤3). All patients in both groups received open-label ASA on day 1 to 90 (50-325 mg depending upon the discretion of the treating physician). Patients randomly assigned to the clopidogrel group received a loading dose of 600 mg of clopidogrel on day 1, followed by 75 mg of clopidogrel per day on days 2 through 90. Patients randomly assigned to the placebo group received clopidogrel placebo on days 1 through 90. The primary efficacy outcome was a composite of major ischemic events (IS, MI or death from an ischemic vascular event) at day 90. This occurred in 121 patients (5.0%) receiving clopidogrel plus ASA compared with 160 patients (6.5%) receiving ASA alone (HR, 0.75; 95% CI, 0.59 to 0.95; P = 0.02). The secondary outcome of IS occurred in 112 patients (4.6%) receiving clopidogrel plus ASA compared with 155 patients (6.3%) receiving ASA alone (HR, 0.72; 95% CI, 0.56 to 0.92; P = 0.01). The primary safety outcome of major hemorrhage occurred in 23 of 2,432 patients (0.9%) receiving clopidogrel plus ASA and in 10 of 2,449 patients (0.4%) receiving ASA alone (HR, 2.32; 95% CI, 1.10 to 4.87; P = 0.02). Minor hemorrhage occurred in 40 patients (1.6%) receiving clopidogrel plus ASA and in 13 (0.5%) receiving ASA alone (HR, 3.12; 95% CI, 1.67 to 5.83; P = 0.001).

CHANCE and POINT Time Course Analysis

There was no efficacy benefit of continuing DAPT beyond 21 days. A time-course distribution of major ischemic events and major hemorrhages by treatment assignment was done to analyze the impact of the short-term time-course of DAPT.

Table 1- Time course distribution of major ischemic events and major hemorrhages by treatment assignment in CHANCE and POINT

No. of events					
Outcomes In CHANCE and POINT	Treatment assignment	Total	1st week	2nd week	3rd week
Major ischemic events	ASA (n=5,035) CLP+ASA(n=5,016) Difference	458 328 130	330 217 113	36 30 6	21 14 7
Major Hemorrhage	ASA (n=5,035) CLP+ASA(n=5,016) Difference	18 30 -12	4 10 -6	2 4 -2	1 2 -1

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 ischemic 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 x 109/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 Aclotil 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-to-pulmonary 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 cardiacrelated 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) (see section 4.2). 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.

5.2 Pharmacokinetic properties

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 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-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. The Cmax of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. Cmax occurs approximately 30 to 60 minutes after dosing.

Elimination

Following an oral dose of 14C-labelled clopidogrel 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-oxoclopidogrel 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 µM 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 thesespecial 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 (see Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

5.3 Preclinical safety data
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.

6. Pharmaceutical particulars
6.1 List of excipients

Ingredients Grade
1 Hydrogenated Castor Oil BP
2 Dichloromethane BP
3 Acetone BP
Extra Granular
4 Microcrystalline Cellulose (PH 112) BP
5 Lactose Anhydrous(DCL-21) USP/NF

6 Pregelatinized Starch USP/NF
7 Polyethylene glycol 6000 (Powder) USP
8 Colloidal Silicon Dioxide USP/NF
9 Purified Talc BP
10 Crospovidone USP/NF
11 Hypromellose (15 CPS) BP
12 Titanium Dioxide BP
13 Dichloromethane BP
14 Isopropyl Alcohol BP
15 Purified Talc BP
16 Propylene Glycol BP
17 Colour Red Oxide of Iron IH
18 Polyethylene glycol 6000 (Powder) USP

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 Months

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

6.5 Nature and contents of container
Primary Packing Material
3x10 Alu-PVC Blister

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder
BAL PHARMA LIMITED
21 & 22, Bommasandra Industrial
Area, Bangalore - 560 099, INDIA