Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Clopraz (Clopidogrel Tablets USP 75mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Clopidogrel bisulfate USP
Equivalent to Clopidogrel 75mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light brown, circular, slightly biconvex film coated tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopidogrel is indicated for the prevention of atherothrombotic events in:

- Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

- Patients suffering from non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) in combination with acetylsalicylic acid (ASA).

For further information please refer to section 5.1.

4.2 Posology and method of administration

- Adults and elderly

Clopidogrel should be given as a single daily dose of 75 mg with or without food.

In patients with 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 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 (see section 5.1).

- Children and adolescents: There is no experience in children.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of the medicinal product.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Due to the risk of bleeding and haematological undesirable effects, 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 4.8). 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, non-steroidal anti-inflammatory drugs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors or thrombolytics. 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 warfarin 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 not necessary, clopidogrel should be discontinued 7 days prior to surgery. 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. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterized by thrombocytopenia and microangiopathic hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

In view of the lack of data, in patients with acute myocardial infarction with ST-segment elevation, clopidogrel therapy should not be initiated within the first few days following myocardial infarction.

In view of the lack of data, clopidogrel cannot be recommended in acute ischaemic stroke (less than 7 days).

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

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: the concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleedings (see section 4.4).

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors. (See section 4.4)

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 (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).

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 (see section 4.4).

Thrombolytics: the safety of the concomitant administration of clopidogrel, rt-PA and heparin was assessed in patients with recent myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when rt-PA and heparin are co-administered with ASA. The safety of the concomitant administration of clopidogrel with other thrombolytic agents has not been formally established and should be undertaken with caution (see section 4.4).

Non-Steroidal Anti-Inflammatory Drugs (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 (see section 4.4).

Other concomitant therapy: a number of other clinical studies have been conducted with clopidogrel and other concomitant medications 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, cimetidine, 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 studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P450 2C9. This could potentially lead to increased plasma levels of drugs such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by Cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

Apart from the specific drug interaction information described above, interaction studies with clopidogrel and some drugs commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medications including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Pregnancy
As no clinical data on exposed pregnancies 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).

Lactation
Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this medicinal product is excreted in human milk.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects Clinical studies experience:

Clopidogrel has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1 year or more. Clopidogrel 75 mg/day was well tolerated compared to ASA 325 mg/day in CAPRIE. The overall tolerability of clopidogrel in this study was similar to ASA, regardless of age, gender and race. The clinically relevant adverse effects observed in the CAPRIE and CURE studies are discussed below.

Hemorrhagic disorders:

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 1.4% for clopidogrel and 1.6% for ASA.

In patients that received clopidogrel, gastrointestinal bleeding occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients that received ASA, the corresponding rates were 2.7% and 1.1%, respectively.

The incidence of other bleedings was higher in patients that received clopidogrel compared to ASA (7.3% vs. 6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% vs. 0.4%). The most frequently reported events in both treatment groups were: purpura/bruising/haematoma, and epistaxis. Other less frequently reported events were haematoma, haematuria, and eye bleeding (mainly Conjunctival).

The incidence of intracranial bleeding was 0.4% in patients that received clopidogrel and 0.5% for patients that received ASA.

In CURE, the administration of clopidogrel+ASA as compared to placebo+ASA was not associated with a statistically significant increase in life-threatening bleeds (event rates 2.2% vs. 1.8%) or fatal bleeds (0.2% vs. 0.2%), but the risk of major, minor and other bleedings was significantly higher with clopidogrel+ASA: non-life-threatening major bleeds (1.6% clopidogrel+ASA vs. 1.0% placebo+ASA), primarily gastrointestinal and at puncture sites, and minor bleeds (5.1% clopidogrel+ASA vs. 2.4% placebo+ASA). The incidence of intracranial bleeding was 0.1% in both groups.

The major bleeding event rate for clopidogrel+ASA was dose-dependent on ASA (□100mg: 2.6%; 100-200mg: 3.5%; □200mg: 4.9%) as was the major bleeding event rate for placebo+ASA (□100mg: 2.0%; 100-200mg: 2.3%; □200mg: 4.0%).

The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months [clopidogrel: 599/6259 (9.6%); placebo: 413/6303 (6.6%)], 1-3 months [clopidogrel: 276/6123 (4.5%); placebo: 144/6168 (2.3%)], 3-6 months [clopidogrel: 228/6037 (3.8%); placebo: 99/6048
(1.6%)], 6-9 months [clopidogrel: 162/5005 (3.2%); placebo: 74/4972 (1.5%)], 9-12 months
[Clopidogrel: 73/3841 (1.9%); placebo: 40/3844 (1.0%)].

There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel+ASA vs. 5.3% placebo+ASA). In patients who remained on therapy within

five days of bypass graft surgery, the event rate was 9.6% for clopidogrel+ASA, and 6.3% for placebo+ASA.

Haematological disorders:

In CAPRIE, severe neutropenia (<0.45 x 10^9/l) was observed in 4 patients (0.04%) that received clopidogrel and 2 patients (0.02%) that received ASA. Two of the 9599 patients who received clopidogrel and none of the 9586 patients who received ASA had neutrophil counts of zero. One case of aplastic anaemia occurred on clopidogrel treatment.

The incidence of severe thrombocytopenia (<80 x 10^9/l) was 0.2% on clopidogrel and 0.1% on ASA.

In CURE, the numbers of patients with thrombocytopenia (19 clopidogrel+ASA vs. 24 placebo+ASA) or neutropenia (3 vs. 3) were similar in both groups.

Other clinically relevant adverse drug reactions pooled from CAPRIE and CURE studies with an incidence ≥ 0.1% as well as all serious and relevant ADR are listed below according to the World Health Organization classification. Their frequency is defined using the following conventions: common (> 1/100, <1/10); uncommon (> 1/1,000, < 1/100); rare (>1/10,000, <1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Central and peripheral nervous system disorders:
- Uncommon: Headache, Dizziness and Paresthesia
- Rare: Vertigo

Gastrointestinal system disorders
- Common: Diarrhea, , Abdominal pain, Dyspepsia
- Uncommon: Gastric ulcer and Duodenal ulcer, Gastritis, Vomiting, Nausea, Constipation, Flatulence.

Platelet, bleeding and clotting disorders
- Uncommon: Bleeding time increased and Platelets decreased

Skin and appendages disorders:
- Uncommon: Rash and Pruritus

White cell and RES disorders
- Uncommon: Leucopenia, Neutrophils decreased and Eosinophilia

Post-marketing experience:

Bleeding is the most common reaction reported in the post-marketing experience and was mostly reported during the first month of treatment.

Bleeding: some cases were reported with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage); serious cases of skin bleeding (purpura), musculo-skeletal bleeding (haemarthrosis, haematoma), eye bleeding (conjunctival, ocular, retinal), epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), haematuria and haemorrhage of operative wound have been reported; cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with acetylsalicylic acid or clopidogrel with acetylsalicylic acid and heparin (see section 4.4).

In addition to clinical studies experience, the following adverse reactions have been spontaneously reported. Within each system organ class (MedDRA classification), they are ranked under heading of frequency. "Very rare" corresponds to <1/10,000. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders:
- Very rare: Thrombotic Thrombocytopenic Purpura (TTP) (1/200,000 exposed patients) (see section 4.4), severe Thrombocytopenia (platelet count $\leq 30 \times 10^9$/l), Agranulocytosis, Granulocytopenia, Aplastic Anaemia/Pancytopenia, Anaemia.

Immune system disorders:
- Very rare: Anaphylactoid reactions, Serum sickness

Psychiatric disorders:
- Very rare: Confusion, Hallucinations

Nervous system disorders:
- Very rare: Taste disturbances

Vascular disorders:
- Very rare: Vasculitis, Hypotension

Respiratory, thoracic and mediastinal disorders:
- Very rare: Bronchospasm, Interstitial pneumonitis

Gastrointestinal disorders:
- Very rare: Pancreatitis, Colitis (including ulcerative or lymphocytic colitis), Stomatitis

Hepato-biliary disorders
- Very rare: Acute liver failure, Hepatitis

Skin and subcutaneous tissue disorders:
- Very rare: Angioedema, Bullous dermatitis (erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis), Rash erythematous, Urticaria, Eczema and Lichen planus

Musculoskeletal, connective tissue and bone disorders:

- Very rare: Arthralgia, Arthritis, and Myalgia.

Renal and urinary disorders:
- Very rare: Glomerulonephritis.

General disorders and administration site conditions
- Very rare: Fever.

Investigations:
- Very rare: Abnormal liver function test, Blood creatinine increase

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: BO1AC/04.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover.

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.

The safety and efficacy of clopidogrel in preventing vascular ischaemic events have been evaluated in two double-blind studies: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE study, a comparison of clopidogrel in combination with ASA, to placebo with ASA.

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 randomized 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 1000 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). 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). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patient's ≤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.

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 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 PTCA with or without stent and 10% when they underwent 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 (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 ischaemia) was 1035 (16.5%) in the clopidogrel-treated group and 1187 (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 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**.** The benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering drugs, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily).

5.2 Pharmacokinetic properties

After repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. However, plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/l) beyond 2 hours. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative, which represents about 85% of the circulating compound in plasma. Peak plasma levels of this metabolite (approx. 3mg/l after repeated 75 mg oral doses) occurred approximately 1 hour after dosing.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by Cytochrome P450 isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

The kinetics of the main circulating metabolite were linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.

Clopidogrel and the main circulating 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.

Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. The elimination half- life of the main circulating metabolite was 8 hours after single and repeated administration.

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 ml/min) and to levels observed in other studies with healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

The pharmacokinetics and pharmacodynamics of clopidogrel were assessed in a single and multiple dose study in both healthy subjects and those with cirrhosis (Child-Pugh class A or B). Daily dosing for 10 days with clopidogrel 75 mg/day was safe and well tolerated. Clopidogrel C_{max} for both single dose and steady state for cirrhotics was many fold higher than in normal subjects. However, plasma levels of the main circulating metabolite together with the effect of clopidogrel on ADP-induced platelet aggregation and bleeding time were comparable between these groups.

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

Tablet Core:
Colloidal Anhydrous Silica
Povidone
Maize Starch
Lactose
Magnesium Stearate
Microcrystalline Cellulose
Purified Talc
Croscarmellose Sodium
Tablet Core:
Opadry Brown
Isopropyl Alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at temperature not exceeding 30ºC, protect from moisture.

6.5 Nature and content of container

Alu-Alu blister pack of 3 x10 tablets.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Zim Laboratories Limited.
Sadoday Gyan (Ground Floor),
Opp. NADT, Nelson Square,
Nagpur – 440013 India.

8. MARKETING AUTHORISATION NUMBERS
04885/06805/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/01/2020

10. DATE OF REVISION OF THE TEXT
29/06/2023