SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CLOGAN 75 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Active substance:
97.857 mg of clopidogrel hydrogen sulfate, equivalent to 75 mg of clopidogrel.

Excipient(s) with known effect:
Lactose monohydrate (produced from bovine milk)……..2.24 mg
Hydrogenated castor oil……..2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet
Biconvex, unscored, pink film coated tablet

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Secondary prevention of atherothrombotic events

- In adult patients: Previous myocardial infarction, previous stroke, or peripheral arterial disease.

Prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease (such as previous stroke, previous myocardial infarction, peripheral arterial disease).

- In adult patients: Acute coronary syndrome

Reduction of the combined outcome rate of cardiovascular death, myocardial infarction, or stroke, as well as the combined outcome of cardiovascular death, myocardial infarction, stroke, or refractory ischemia in patients with acute coronary syndrome (unstable angina without ST segment elevation or non-Q-wave myocardial infarction or acute myocardial infarction with ST segment elevation), including those who need to be treated medically or who have had percutaneous coronary intervention (with or without stent) or coronary artery bypass graft surgery (CABG).

- Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

Clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke, in adult patients with atrial fibrillation who have at least one risk factor for vascular events, could not receive Vitamin K Antagonist (VKA) therapy, and are at low bleeding risk.

4.2. Posology and method of administration

Posology/Frequency and duration of administration:
Adults

- Previous myocardial infarction, previous stroke, or peripheral arterial disease

Clopidogrel should be given as a single 75 mg dose.

- Acute Coronary Syndrome

In patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave myocardial infarction), clopidogrel therapy should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily over the long term (with acetylsalicylic acid (ASA) 75 mg - 325 mg daily). Since high doses of ASA are associated with an increased risk of bleeding, it is recommended that the ASA dose not exceed 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use for up to 12 months, with maximum benefit seen at 3 months (see section 5.1).

In patients with acute myocardial infarction with ST segment elevation, treatment with clopidogrel should be initiated with a single 300 mg loading dose either in combination with thrombolytics or in combination with ASA alone, and continued at 75 mg once daily. Combination therapy should be started as early as possible after symptoms begin and continued for at least four weeks. The benefit of using clopidogrel with ASA for more than four weeks has not been studied (see Section 5.1 Pharmacodynamic Properties).

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).

Method of administration
For oral use.
Clopidogrel can be taken with or between meals.

Additional information on special populations:
Renal impairment / Hepatic impairment
Therapeutic experience with clopidogrel is limited in patients with severe and moderate renal impairment. Therefore, clopidogrel should be used with caution in these patients (see section 4.4). Experience is limited in patients with moderate hepatic impairment who may have bleeding diatheses. Therefore, clopidogrel should be used with caution in this population (see section 4.4). It should not be used in patients with severe hepatic impairment (see section 4.3).

Pediatric population
Clopidogrel should not be used in children and adolescents as its safety and efficacy have not been established.

Geriatric population
In patients over 75 years of age with acute myocardial infarction with ST segment elevation, treatment with clopidogrel should be initiated without a loading dose.

Pharmacogenetics
CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. An appropriate dose regimen for poor metabolizers has not been established (see section 5.2).

4.3. Contraindications

- Hypersensitivity to the active substance or excipients in the composition of the medicine
- Severe hepatic disease
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage

4.4. Special warnings and precautions for use

Bleeding and hematological disorders
Due to the risk of bleeding and hematological 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 4.8 Undesirable Effects).

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, 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 (see section 4.5 Interaction with other medicinal products and other forms of interaction).

If a patient is undergoing elective surgery and an antiaggregant effect is not desired, clopidogrel should be discontinued 7 days before surgery.

The combination of ASA and clopidogrel has been shown to increase major bleeding in patients with a high risk of recurrent ischemic events and a recent transient ischemic attack or stroke. Therefore, caution should be exercised in administering such a combination, except in clinical situations where benefit has been proven.

As clopidogrel prolongs bleeding time, it should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Patients should be advised that bleeding that may occur during the use of clopidogrel (alone or in combination with ASA) can be stopped longer than usual and that they should report any unusual bleeding (location or duration) to their physician. Patients should inform their physician and dentist that they are using clopidogrel before any surgery is planned and before any new medication is started.

Concomitant use of omeprazole or esomeprazole with CLOGAN should be avoided. The use of another acid-lowering drug that has no or minimal CYP2C19 inhibitory effect on the formation of the active metabolite of clopidogrel should be considered. Lansoprazole and pantoprazole have less effect on the antiplatelet activity of CLOGAN than omeprazole or esomeprazole.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has rarely been reported following the use of clopidogrel, sometimes within a short period of time (< 2 weeks). TTP is a potentially fatal condition requiring prompt treatment with plasmapheresis. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (fragmented schistocyte (fragmented erythrocytes) may be seen in peripheral smear), neurological findings, renal dysfunction and fever.

Recent ischemic stroke:
Due to the lack of data, the use of clopidogrel during the first 7 days of acute ischemic stroke cannot be recommended.

Acquired hemophilia
Acquired hemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired hemophilia should be considered. Patients with a confirmed diagnosis of acquired hemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Cytochrome P450 2C19 (CYP2C19):
Pharmacogenetics: In patients who are poor CYP2C19 metabolizers, 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 metabolized 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 medicines containing CYP2C8 substrates (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 (hematological reactions such as rash, angioedema, or thrombocytopenia and neutropenia). Patients who had developed a previous allergic reaction and/or hematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of cross-hypersensitivity 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
CLOGAN contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains hydrogenated castor oil, which may cause nausea and diarrhea.

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 (see section 4.4).

Oral anticoagulants:
The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.4). Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalized 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 (see section 4.4).

Acetylsalicylic acid (ASA)
Acetylsalicylic acid did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of acetylsalicylic acid on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of acetylsalicylic acid 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 of clopidogrel and heparin should be undertaken with caution (see section 4.4).

Thrombolytics
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. However, caution should be exercised when using clopidogrel with thrombolytic agents (see section 4.8).

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).

Selective Serotonin Reuptake Inhibitors (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 therapies
Since clopidogrel is metabolized 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. 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 CYP2C19 inhibitors include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton pump inhibitors (PPI)
Concomitant use of omeprazole or esomeprazole with CLOGAN should be avoided. The use of another acid-lowering drug that has no or minimal CYP2C19 inhibitory effect on the formation of the active metabolite of clopidogrel should be considered. Lansoprazole and pantoprazole have less effect on the antiplatelet activity of CLOGAN than omeprazole or esomeprazole.

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/pharmacodynamic 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 H_2 blockers (except cimetidine, which is a CYP2C19 inhibitor) 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 medicines
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 estrogen.

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 on human liver microsomes indicate that the carboxylic acid metabolite of clopidogrel can inhibit CYP2C9 activity. This may potentially lead to increased plasma levels of drugs metabolized by CYP2C9, such as phenytoin, tolbutamide, tamoxifen, torsemide, fluvastatin, and NSAIDs. Data from the CAPRIE study indicate that phenytoin and tolbutamide, which are metabolized by CYP2C9, can be safely used in combination with clopidogrel.

CYP2C8 substrates
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).

In addition to the specific interaction studies mentioned above, in patients participating in clinical trials of clopidogrel and taking many different medicines simultaneously (diuretics, beta-blockers, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol-lowering medicines, coronary vasodilators, antidiabetic agents, hormone replacement therapy) no clinically significant adverse interactions were observed.

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. The use of a parenteral antiplatelet agent should be considered in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists

Additional information on the special populations
No data are available for specific populations.

Pediatric population
No data are available for pediatric population.

4.6. Fertility, pregnancy and lactation

General recommendation
Pregnancy category: B

Women of childbearing potential / Contraception
In women of childbearing potential, it would be appropriate to use medically effective methods of contraception during treatment.

Pregnancy
There are insufficient data on the use of clopidogrel in pregnant women. As a precaution, it is recommended that CLOGAN be avoided during pregnancy unless the benefit outweighs the risks.

No clinical data on exposure to clopidogrel during pregnancy are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3).

Breastfeeding
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 CLOGAN.

Reproductive ability / Fertility
Reproductive studies in rats and rabbits did not show impairment of fertility or harm to the fetus due to clopidogrel (see section 5.3 Preclinical safety data).

4.7. Effects on ability to drive and use machines

No impairment in driving ability or psychometric performance has been observed after administration of clopidogrel. Patients can drive and operate machinery during clopidogrel therapy.

4.8. Undesirable effects

Clinical experience
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 (Clopidogrel 1.4%, ASA 1.6%).

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.

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are listed below according to system-organ classification and incidence. Their incidence is defined as: Very common (≥ 1/10); 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)

Blood and the lymphatic system disorders
Uncommon: Thrombocytopenia, leucopenia, eosinophilia
Rare: Neutropenia, including severe neutropenia
Very rare: Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anemia acquired hemophilia A

Immune system disorders
Very rare: Anaphylactic reactions, serum sickness
Not known: Cross-reactive drug hypersensitivity between thienopyridines (e.g. ticlopidine, prasugrel) (see section 4.4), insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with the HLA DRA4 subtype (more frequent in the Japanese population).

Psychiatric disorders
Very rare: Confusion, hallucinations

Nervous system disorders
Uncommon: bleeding (some cases were reported with fatal outcome), headache, dizziness, paresthesia.
Very rare: Taste disturbances, ageusia (inability to taste)

Eye disorders
Uncommon: Eye bleeding (conjunctival, ocular, retinal)

Ear and labyrinth disorders
Rare: Vertigo

Cardiac disorders
Not known: Kounis syndrome (Vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction to clopidogrel.

Vascular disorders
Common: Hematoma
Very rare: Serious hemorrhage, hemorrhage of operative wound, vasculitis, hypotension

Respiratory, thoracic and mediastinal disorders
Common: Epistaxis
Very rare: Respiratory tract bleeding (hemoptysis, pulmonary hemorrhage), bronchospasm, interstitial pneumonia, eosinophilic pneumonia

Gastrointestinal disorders
Common: Gastrointestinal hemorrhage, dyspepsia, abdominal pain, diarrhea

Uncommon: Nausea, gastritis, flatulence, constipation, vomiting, gastric ulcer, duodenal ulcer
Rare: Retroperitoneal hemorrhage
Very rare: Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative and lymphocytic colitis), stomatitis

Hepato-biliary disorders
Very rare: Hepatitis, acute liver failure, abnormal liver function test

Skin and subcutaneous tissue disorders
Common: Bruising
Uncommon: Rash, pruritus, skin bleeding (purpura)
Very rare: Erythematous or exfoliative rash, urticaria, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson Syndrome, acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrolysis), drug-induced hypersensitivity syndrome, eosinophilia and systemic symptoms rash (DRESS), eczema, lichen planus

Reproductive system and breast disorders
Rare: Gynecomastia

Musculoskeletal, connective tissue and bone disorders
Very rare: Musculoskeletal bleeding (hemarthrosis), arthralgia, arthritis, myalgia

Renal and urinary disorders
Uncommon: Hematuria
Very rare: Glomerulonephritis, blood creatinine increased

General disorders and administration site conditions
Common: Bleeding at puncture site
Very rare: Fever

Investigations
Uncommon: Bleeding time prolonged, neutrophil count decreased, platelet count decreased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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 excluding heparin
ATC Code: B01AC04.

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

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

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 in these studies).

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 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 five days following the acute myocardial infarction

Clopidogrel significantly reduced the incidence of new ischemic events (combined endpoint of myocardial infarction, ischemic stroke and vascular death) when compared to ASA. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6%).

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 randomized to clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo, both given in combination with ASA (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year.

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% Confidence Interval 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 coronary surgery with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events were prevented. 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 Special warnings and precautions for use).

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% confidence interval of 6%-21%, p=0.0005) for the clopidogrel-treated group.

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 revascularization, age, gender, etc.) were consistent with the results of the primary analysis. 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 (STEMI), safety and efficacy of clopidogrel have been evaluated in 2 randomized, 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.

15% 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: 0.53, 0.76, 47%; $p < 0.001$).

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.

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).

De-escalation of $P2Y_{12}$ Inhibitor Agents in Acute Coronary Syndrome
Switching from a more potent $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 two 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).

Atrial fibrillation
The ACTIVE-W and ACTIVE-A studies, separate trials in the ACTIVE program, included patients with atrial fibrillation 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 + ASA.

In the ACTIVE-A study (N=7,554), which was a multicenter, randomized, double-blind, placebo-controlled study, clopidogrel 75 mg/day + ASA (N=3,772) were compared 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 atrial fibrillation, i.e., either permanent atrial fibrillation 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 (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 10^9/l); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance to any of the two compounds.

73% of patients enrolled into the ACTIVE-A study were unable to take VKA. 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).

The reduction in the risk of major vascular events in the clopidogrel + ASA-treated group is primarily due to the significant reduction in stroke incidence. 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).

Pediatric 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 mcM ADP-induced platelet aggregation) which was comparable to that of adults taking clopidogrel 75 mg/day. In a randomized, double-blind, parallel-group study (CLARINET), 906 pediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomized 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 acetylsalicylic acid (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) (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 authorized tablet.

5.2. Pharmacokinetic properties

General 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 (up to concentration of 100 mg/l).

Biotransformation
Clopidogrel is extensively metabolized by the liver. *In vitro* and *in vivo*, clopidogrel is metabolized according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (carboxylic acid derivative represents 85% of circulating metabolites 85% of circulating metabolites), and one mediated by multiple cytochromes P450.

Clopidogrel is first metabolized 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. This metabolite could not be isolated in plasma.

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 ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the feces 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.

Additional information on special populations
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 metabolizers.

A patient with poor metabolizer status will possess two loss-of-function alleles as defined above. Published frequencies for the poor CYP2C19 metabolizer 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 metabolizer 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 metabolizers. In poor metabolizers, active metabolite exposure was decreased by 63-71% compared to extensive metabolizers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolizers with mean IPA (5 mcM ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolizers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolizers. When poor metabolizers 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 metabolizers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metabolizer groups receiving the 300 mg/75 mg regimen.

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 metabolizers, and 72% for poor metabolizers while platelet aggregation inhibition (5

μM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolizers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomized, 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 three of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers.

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

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

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

Special populations
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.

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.

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Gender:
In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but no difference in prolongation of bleeding time. In a large, controlled clinical trial (aspirin versus clopidogrel in patients at risk for ischemic events, CAPRIE); the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters were similar in men and women.

Elderly:
There was no difference in platelet aggregation and bleeding time in elderly (≥ 75 years) volunteers compared to young healthy volunteers. No dosage adjustment is required in the elderly.

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 metabolizing enzymes. No effect on hepatic metabolizing 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 radiolabeled 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:
Mannitol
Pregelatinized starch
Silicified microcrystalline cellulose
Hydrogenated castor oil
Hydroxypropylcellulose

Opadry II Pink (Film Coating):
Hypromellose
Lactose monohydrate (produced from bovine milk)
Triacetin
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

Alu / Alu blister packs.
Each cardboard box contains 14, 28 or 90 tablets.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment.

7. MARKETING AUTHORISATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece - ISTANBUL/TURKEY

8. MARKETING AUTHORISATION NUMBER

231/65

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Date of first authorization : 06.05.2011
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

24.12.2020