Public Assessment Report

Decentralised Procedure

Clopez 75 mg film-coated tablets
(clopidogrel bisulphate)

Procedure No: UK/H/3606/001/DC

UK Licence No: PL 34088/0002

Alkaloid-INT d.o.o.
Clopez 75 mg film-coated tablets

LAY SUMMARY

On 22 March 2012, the UK granted a Marketing Authorisation to Alkaloid-INT d.o.o. for the medicinal product Clopez 75 mg film-coated tablets (PL 34088/0002; UK/H/3606/001/DC). This is a prescription-only medicine (POM) used to prevent blood clots (thrombi) forming in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

Clopez 75 mg film-coated tablets are prescribed to help prevent blood clots and reduce the risk of these severe events in patients who have:

- a condition of hardening of arteries (also known as atherosclerosis), and….
- previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease, or ….
- who have experienced a severe type of chest pain known as ‘unstable angina’ or ‘myocardial infarction’ (heart attack). For the treatment of this condition the doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. The patient should also be given acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever as well as to prevent blood clotting) by the doctor, or….
- who have an irregular heartbeat, a condition called ‘atrial fibrillation’, and who cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. The patient should have been told that ‘oral anticoagulants’ are more effective than acetylsalicylic acid or the combined use of Clopez 75 mg film-coated tablets and acetylsalicylic acid for this condition. The doctor should have prescribed Clopez 75 mg film-coated tablets plus acetylsalicylic acid if the patient cannot take ‘oral anticoagulants’ and does not have a risk of major bleeding.

Clopez 75 mg film-coated tablets belong to a group of medicines known as antiplatelet medicinal products. Platelets are very small structures, smaller than red or white blood cells, which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clots forming (a process called thrombosis).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Clopez 75 mg film-coated tablets outweigh the risks and a Marketing Authorisation was granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Patient Information Leaflet</td>
<td>18</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>20</td>
</tr>
<tr>
<td>Module 5: Scientific discussion during initial procedure</td>
<td>21</td>
</tr>
<tr>
<td>I Introduction</td>
<td></td>
</tr>
<tr>
<td>II About the product</td>
<td></td>
</tr>
<tr>
<td>III Scientific overview and discussion</td>
<td></td>
</tr>
<tr>
<td>III 1 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>III 2 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>III 3 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>IV Overall conclusion and benefit/risk assessment</td>
<td></td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td></td>
</tr>
</tbody>
</table>
# Module 1

**Information about the initial procedure**

<table>
<thead>
<tr>
<th>Product Names</th>
<th>Clopez 75 mg film-coated tablets</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Clopidogrel bisulphate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>75 mg</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Alkaloid-INT d.o.o.</td>
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<tr>
<td></td>
<td>Šlandrova ulica 4</td>
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<tr>
<td></td>
<td>1231 Ljubljana – Črnuče, Slovenia</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Bulgaria, Czech Republic, Romania, Slovak Republic and Slovenia</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/3606/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 08 February 2012</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
CLOPEZ 75 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 75 mg clopidogrel (in a form of clopidogrel hydrogen sulphate)
Also contains: each film-coated tablet contains 96.495 mg lactose, monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
* Film-coated tablet.
Red-pink coloured, round, biconvex, film-coated tablets with debossed Latin letter C on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Prevention of atherothrombotic events
Clopidogrel is indicated in:
- Adult 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.
- 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.

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.

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 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 (see section 5.1).

- 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 (see section 5.1).

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 patients**
Clopidogrel should not be used in children because of efficacy concerns (see section 5.1).

**Renal impairment**
Therapeutic experience is limited in patients with renal impairment (see section 4.4).

**Hepatic impairment**
Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4).

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

### 4.3 Contraindications
- Hypersensitivity to clopidogrel or to any of the excipients of the medicinal product.
- 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 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, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors. 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.

**Recent ischaemic stroke**
In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

**Cytochrome P450 2C19 (CYP2C19)**
Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient’s CYP2C19 genotype.
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5 for a list of CYP2C19 inhibitors, see also section 5.2).

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
Clopez contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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 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 (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, 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 (see section 4.8).

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. 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 inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

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 esomeprozole should be discouraged (see section 4.4.).

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 (except cimetidine which is a CYP2C19 inhibitor) or antacids interfere with antiplatelet activity of clopidogrel.

Other medicinal products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

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.

### 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).

**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 Clopez.
**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**
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 haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

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). Within each system organ class, adverse drug reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Thrombocytopenia, leucopenia, eosinophilia</td>
<td>Neutropenia, including severe neutropenia</td>
<td>Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia</td>
<td></td>
</tr>
</tbody>
</table>
## Side effects

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Serum sickness, anaphylactoid reactions</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hallucinations, confusion</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Taste disturbances</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
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<td>Vertigo</td>
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<td>Vascular disorders</td>
<td></td>
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</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
<td>Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis</td>
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<tr>
<td>Gastrointestinal disorders</td>
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<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Acute liver failure, hepatitis, abnormal liver function test</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
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<td></td>
<td>Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous, urticaria, eczema, lichen planus</td>
</tr>
<tr>
<td>Musculoskeletal connective tissue and bone disorders</td>
<td></td>
<td></td>
<td></td>
<td>Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Glomerulonephritis blood creatinine increased</td>
</tr>
</tbody>
</table>

- **Common**: Symptoms that occur in more than 1/10 patients
- **Uncommon**: Symptoms that occur in 1/10 to 1/100 patients
- **Rare**: Symptoms that occur in less than 1/100 patients
- **Very rare**: Symptoms that occur in less than 1/1000 patients
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: B01AC04.

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.

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

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

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

Clopidogrel significantly reduced the incidence of new ischaemic events (combined end point of myocardial infarction, ischaemic stroke and vascular death) when compared to ASA. In the intention to treat analysis, 939 events were observed in the clopidogrel group and 1,020 events with ASA (relative risk reduction (RRR) 8.7%, [95% CI: 0.2 to 16.4]; p = 0.045), which corresponds, for every 1,000 patients treated for 2 years, to 10 [CI: 0 to 20] additional patients being prevented from experiencing a new ischaemic event. Analysis of total mortality as a secondary endpoint did not show any significant difference between clopidogrel (5.8%) and ASA (6.0%).
In a subgroup analysis by qualifying condition (myocardial infarction, ischaemic stroke, and PAD) the benefit appeared to be strongest (achieving statistical significance at p = 0.003) in patients enrolled due to PAD (especially those who also had a history of myocardial infarction) (RRR = 23.7%; CI: 8.9 to 36.2) and weaker (not significantly different from ASA) in stroke patients (RRR = 7.3%; CI: -5.7 to 18.7 [p=0.258]). In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel was numerically inferior, but not statistically different from ASA (RRR = -4.0%; CI: -22.5 to 11.7 [p=0.639]). In addition, a subgroup analysis by age suggested that the benefit of clopidogrel in patients over 75 years was less than that observed in patients ≤ 75 years.

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

**Acute coronary syndrome**

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

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the clopidogrel-treated group (17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)). New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel + ASA group was not further increased, whereas the risk of haemorrhage persisted (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 benefits observed with clopidogrel were independent of other acute and long-term cardiovascular therapies (such as heparin/LMWH, GPIIb/IIIa antagonists, lipid lowering medicinal products, beta blockers, and ACE-inhibitors). The efficacy of clopidogrel was observed independently of the dose of ASA (75 – 325 mg once daily).
In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1,752) or placebo (n=1,739), both in combination with ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients \( \geq 65 \) 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 \( \geq 60 \) years (26% \( \geq 70 \) 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.

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, placebo-controlled 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 \( \geq 75 \) years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction <45%; or documented peripheral vascular disease. The mean CHADS2 score was 2.0 (range 0 -6).

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

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

The patient population included 41.8% women. The mean age was 71 years, 41.6% of patients were ≥75 years. A total of 23.0% of patients received anti-arrhythmics, 52.1% beta-blockers, 54.6% ACE inhibitors, and 25.4% statins.

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

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

In a randomised, double-blind, parallel-group study (CLARINET), 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-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 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 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.

Metabolism
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 the 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. In vitro, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. 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-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype.

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

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μM 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 these special populations.

**Renal impairment**

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

**Hepatic impairment**

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

**Race**

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (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.

### Preclinical safety data

During nonclinical 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 has been 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.

### PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core:**
- Lactose Monohydrate;
- Maize starch, partially pregelatinised;
- Croscarmellose Sodium;
- Povidone;
- Silica Colloidal, Anhydrous;
- Butylhydroxytoluene (E321);
- Glycerol dibehenate.

**Film coating**
- Hypromellose;
- Cellulose microcrystalline;
- Titanium dioxide (E 171);
- Colour red iron oxide (E 172).
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months.

6.4 Special precautions for storage
Store at a temperature below 25°C. Store in the original package.

6.5 Nature and contents of container
The film coated tablets are immediate packed in press-through blisters (PVC/TE/PVdc/Aluminium), containing 10 tablets on each blister.
The lithographed cardboard box containing 30 tablets (3 blisters) and an instruction leaflet.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
ALKALOID-INT d.o.o.
Šlandrova ulica 4
1231 Ljubljana – Črnuče,
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 34088/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/03/2012

10 DATE OF REVISION OF THE TEXT
22/03/2012
Package leaflet: Information for the user

CLOPENG 75 mg film-coated tablets

Clopez 75 mg film-coated tablets

UK/H/3606/001/DC

18

Module 3
Patient Information Leaflet

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need it again.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others, even if their symptoms are the same as yours.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Clopez is and what it is used for
2. Before you take Clopez
3. How to take Clopez
4. Possible side effects
5. How to store Clopez
6. Further information

1. WHAT CLOPEZ IS AND WHAT IT IS USED FOR

Clopez belongs to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood which clump together during blood clotting. By preventing this clumping, antiplatelet medicinal products reduce the chances of blood clot formation (a process called thrombosis).

Clopez is taken to prevent blood clot (thrombus) formation in hardened blood vessels (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack, or death).

You have been prescribed Clopez to help prevent blood clots and reduce the risk of these severe events because:

- You have conditions such as narrowing of arteries (also known as atherosclerosis), and
- You have recently experienced a heart attack, stroke, or have had a heart attack or have had a heart attack or
- You have experienced a severe type of chest pain known as "unstable angina" or "myocardial infarction" (heart attack).

For the treatment of this condition your doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. You should also be given a thiacloprid and a substance present in many medicines used to reduce pain and prevent or treat pain and prevent or treat pain.

2. BEFORE YOU TAKE CLOPENG

Do not take Clopez:

- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients,
- If you have a medical condition that is currently causing bleeding such as a stroke or bleeding within the liver,
- If you suffer from severe liver disease.

If you think any of these apply to you, or if you are in any doubt at all, consult your doctor before taking Clopez.

Take special care with Clopez

If any of the situations mentioned above apply to you, you should tell your doctor before taking Clopez:

- If you have a risk of bleeding such as:
  - a medical condition that puts you at risk of internal bleeding (such as a recent stroke.

- a blood disorder that makes you prone to internal bleeding (bleeding into any tissues, organs or joints of your body)
- a severe allergic reaction
- a recent surgery (including dental)
- a planned surgery (including dental) in the next seven days.
- If you have had a clot in any of your veins (thromboembolic event) which occurred within the last seven days

- If you have history of liver disease.

While you are taking Clopez:

- You should tell your doctor or a surgery (including dental) is planned.
- You should also tell your doctor immediately if you develop a medical condition known as "thrombotic thrombocytopenic purpura or TTP" which includes fever and bruising under the skin that may appear at this point. This medicine includes fever and bruising under the skin that may appear at this point. This medicine.
- If you have had a clot in any of your veins (thromboembolic event) which occurred within the last seven days.
- If you are allergic or have a history of allergy, it may take longer than usual for your bleeding to stop. This is linked to the way your medicine works and it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself while shaving, this is usually no problem. However, if you are concerned about your bleeding, you should contact your doctor immediately (see section 4 "Possible side effects"

- Your doctor may order blood tests.

Clopez is not recommended for use in children or adolescents.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Some other medicines may increase the risk of taking CLOPENG

You should specifically tell your doctor if you take:

- Oral anticoagulants, medicated used to reduce blood clotting.
- A non-steroidal anti-inflammatory medicine, usually used to treat painful and/or inflammator conditions of muscle or joints, and
- Certain other medicines used to reduce blood clotting.

- Flavonoids, flavonoids, flavonoids, flavonoids, flavonoids, flavonoids, flavonoids, flavonoids, flavonoids, flavonoids, flavonoids.

- Thrombosis, thrombosis, thrombosis, thrombosis, thrombosis, thrombosis, thrombosis, thrombosis, thrombosis, thrombosis, thrombosis.

- Clopidogrel, other antiplatelet agents.

If you have experienced severe chest pain (unstable angina or heart attack), you may be prescribed Clopez in combination with a beta-blocker and/or a calcium channel blocker. These medicines may reduce the risk of death or heart attack. However, in patients with severe angina, beta-blockers may not be appropriate for use.

Taking Clopez with food and drink:

Clopez may be taken with or without food:

- Pregnancy and breastfeeding:

It is preferable not to use this product during pregnancy.

If you are pregnant or breast-feeding, you should tell your doctor or pharmacist before taking Clopez. If you become pregnant while taking Clopez, consult your doctor immediately as it is recommended not to take Clopez while you are pregnant.

You should not breastfeed while taking this medicine.

If you are breast-feeding, or planning to breast-feed, talk to your doctor before taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines:

Clopez is unlikely to affect your ability to drive or to use machines.
Important information about some of the ingredients of Clopez
Clopez contains lactose. If you have been told by your doctor that you have an intolerance to some sugars (e.g. lactose), contact your doctor before taking this medicine.

3. HOW TO TAKE CLOPEZ
Always take Clopez exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. If you have experienced severe chest pain (unstable angina or heart attack), your doctor may give you 150 mg or Clopez (4 tablets of 75 mg) once at the start of treatment. Thus, the usual dose is one 75-mg tablet of Clopez per day to be taken only with or without food, and at the same time each day. You should take Clopez for as long as your doctor continues to prescribe it.

If you take more Clopez than you should:
Contact your doctor or the nearest hospital emergency department because of the increased risk of bleeding.

If you forget to take a Clopez:
Do not take double doses to make up for the forgotten individual dose.
If you forget to take a dose of Clopez, but remember within 12 hours of your usual time, take your tablet immediately and then take your next tablet at the usual time.
If you forget for more than 12 hours, simply take the next tablet at the usual time.

If you stop taking Clopez:
Do not stop the treatment unless your doctor tells you to. Contact your doctor or pharmacist before stopping.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Clopez can cause side effects, although not everybody gets them.
The frequency of possible side effects listed below is defined using the following categories:
- very common (affects more than 1 in 10 people)
- common (affects 1 in 10 to 1 in 100 people)
- uncommon (affects 1 in 100 to 1 in 1,000 people)
- rare (affects 1 in 1,000 to 1 in 10,000 people)
- very rare (affects less than 1 in 10,000 people)
- unknown (frequency cannot be estimated from the available data)

Contact your doctor immediately if you experience:
- fever, signs of infections or systemic reactions. These may be due to rare decrease of some blood cells.
- signs of liver problems, such as jaundice, or associated with bleeding which appears under the skin as red pinpoint spots and or oozing (see section "Take special care with Clopez")
- swallowing in the mouth or skin disorders such as rash and itching, blisters or skin problems. These may be the signs of an allergic reaction.

The most common side effects reported with clopidogrel is bleeding. Bleeding may occur as bleeding in the stomach or bowel, bruising, haemorrhage (nosebleeding or bleeding under the skin), nose bleed, blood in urine. In a small number of cases, bleeding in the eye, mouth, the leg or the chest was also reported.

If you experience prolonged bleeding when taking Clopez:
If you can or may injure yourself, it may take slightly longer than usual for bleeding to stop. This is linked to the way your medicines works as it prevents the ability of blood cells to form. For minor cuts and injuries e.g., cutting yourself, shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor and tell him or her about your situation. Take special care with Clopez.

Other side effects reported with clopidogrel are:
Common side effects: Dizziness, abdominal pain, indigestion or heartburn.

Uncommon side effects: Headache, stomach ulcer, vomiting, nausea, constipation, diarrhea, diarhoea, indigestion, sensation of tingling and numbness.

Rare side effect: Vertigo.

Very rare side effects: Jaundice, severe abdominal pain with vomiting, high blood pressure, vision problems, weight loss, muscle weakness, drowsiness, swollen ankles, increased blood sugar, heart attack, stroke, pulmonary embolism, phlebitis, skin rash, increased sensitivity to sunlight.

In addition, your doctor may ask you to see your doctor or pharmacist if any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please consult your doctor or pharmacist.

5. HOW TO STORE CLOPEZ
Keep out of the reach and sight of children.
Do not use Clopez after the expiry date which is stated on the carton or package. The expiry date refers to the last day of that month.
To be stored at a temperature between 2°C and 25°C in the original package.
Medicines should be disposed of by means of water or household waste. Ask your pharmacist how to dispose of medicines as required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Clopez contains:
- The active substance is clopidogrel.
- Each film-coated tablet contains 75 mg clopidogrel (as a form of clopidogrel bisulfate).
- Other ingredients are: Lactose monohydrate; Maize starch, partially pregelatinised; Cornstarch; Silica, Aerosil 200; E671; E171; E172; E174; Acesulfame potassium; Calcium phosphates dibasic; Sodium hydrogen carbonate; Magnesium stearate; Colour E102 (tartrazine).

What Clopez looks like and contents of the pack:
- Clopez 75 mg film-coated tablets are red-pink coloured, round, bi-convex, film-coated tablets with debossed Latin letter "C" on one side.
- The film-coated tablets are imprinted on the faces with "75 mg" and on the backs with "CLOPEZ 75 mg".
- The pack contains 28 tablets (4 blisters) and an instruction leaflet.

Marketing Authorization Holder and Manufacturer:
ALKALOID – INT d.o.o., Štrandnica 14, 1231 Lubiana – Crnica, Slovenia.
Tel. 186 1 000 43 00
Fax 186 1 000 43 91
Email info@alkaloid.si

This medicinal product is authorised in the Member States of the EU under the following names:
- Bulgaria: Clopez 75 mg film-coated tablets
- Czech Republic: Clopez 75 mg peroralní tablety
- Slovak Republic: Clopez 75 mg film-obláhaná tablety
- Slovenia: Clopez 75 mg film-ovičkane tablete
- Romania: Clopez 75 mg comprimate filmate
- UK: Clopez 75 mg film-coated tablets
- US: Clopez 75 mg film-coated tablets, Pl. 40060/0963

Leaflet last revised 02/2011.
Module 4
Labelling

CLOPEZ 75 mg film-coated tablets
Clopidogrel

30 tablets

Each film-coated tablet contains 75 mg of clopidogrel as clopidogrel hydrobromide.
Also contains lactose. Refer to leaflet for further information.
For oral use. Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 25°C. Store in the original package.

POM
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Clopez 75 mg film-coated tablets (PL 34088/0002; UK/H/3606/001/DC) could be approved. The product is a prescription-only medicine (POM) used in adults 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.
  - in 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.

- atherothrombotic and thromboembolic events in atrial fibrillation
  - in 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, in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

This was an abridged complex application submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Bulgaria, Czech Republic, Romania, Slovak Republic and Slovenia as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France), which was registered in the EEA via the Centralised Procedure on 15 July 1998.

Clopez 75 mg film-coated tablets contain the active ingredient, clopidogrel (as clopidogrel bisulphate, also referred to as clopidogrel hydrogen sulphate). Clopidogrel is a thienopyridine molecule analogue which 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.

No new non-clinical studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

One single-dose, bioequivalence study was submitted to support this application, comparing the test product Synetra 75 mg film-coated tablet (Alkaloid AD) versus the reference product Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France). During product development, Synetra 75 mg film-coated tablets (Alkaloid) was the name used for Clopez 75 mg film-coated tablets (Alkaloid-INT d.o.o.). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
With the exception of this bioequivalence study, no new clinical studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 08 February 2012. After a subsequent national phase, the licence was granted in the UK on 22 March 2012.
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Clopez 75 mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name(s) of the active substance(s) (INN)</strong></td>
<td>Clopidogrel bisulphate</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Platelet aggregation inhibitors (excluding heparin) ATC code: (B0AC 04)</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td>75 mg film-coated tablets</td>
</tr>
<tr>
<td><strong>Reference numbers for the Decentralised Procedure</strong></td>
<td>UK/H/3606/001/DC</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Bulgaria, Czech Republic, Romania, Slovak Republic and Slovenia</td>
</tr>
<tr>
<td><strong>Marketing Authorisation Number</strong></td>
<td>PL 34088/0002</td>
</tr>
<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>Alkaloid-Int d.o.o. Šlandrova ulica 4 1231 Ljubljana – Črnuče, Slovenia</td>
</tr>
</tbody>
</table>

### III. SCIENTIFIC OVERVIEW AND DISCUSSION

#### III.1 QUALITY ASPECTS

**ACTIVE SUBSTANCE**

INN: Clopidogrel bisulphate

Chemical names: S(+-)-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno-[3,2-c] pyridine-5-yl) acetic acid methyl ester hydrogen sulphate.

Structure:

![Structure](image)

Molecular formula: C₁₆H₁₆ClNO₂S. H₂SO₄

Molecular Mass: 419.90

Appearance: A white to off-white crystalline powder

Solubility: Freely soluble in methanol, practically insoluble in water and ether.

At the time of initial assessment, clopidogrel bisulphate was not the subject of a European Pharmacopoeia monograph. However, if now tested, clopidogrel bisulphate would meet the specifications of the European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff. Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

**MEDICINAL PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients in the tablet core and film coating, namely lactose monohydrate; maize starch, partially pregelatinised; croscarmellose sodium; povidone; silica, anhydrous colloidal; butylhydroxytoluene (E321); glycerol dibehenate; hypromellose; cellulose microcrystalline; titanium dioxide (E171) and colour red iron oxide (E172). Appropriate justification for the inclusion of each excipient has been provided.

With the exception of red iron oxide (E172), all excipients comply with their respective European Pharmacopoeia monograph. Red iron oxide (E172) is controlled to its National Formulary specification and is in compliance with current European Directives concerning use of colouring agents in foodstuffs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in its production is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material of any kind is used during production.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution and impurity profiles have been provided for this product and the reference product Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full-scale production batches and has shown satisfactory results.

**Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.
Container-Closure System
The product is packaged in PVC/TE/PVdC/Aluminium blisters strips. These are packed into cardboard cartons with patient information leaflets in a pack size of 30 film-coated tablets (3 blisters).

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months has been proposed with the storage conditions ‘Store at a temperature below 25°C. Store in the original package.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA (Marketing Authorisation Application) Form
The MAA form is pharmaceutically satisfactory.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of clopidogrel bisulphate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for the non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS

Clinical pharmacology

The clinical pharmacology of clopidogrel bisulphate is well-known. With the exception of data from the bioequivalence study described below, no new pharmacodynamic or pharmacokinetic data was provided or required for this application.

Pharmacokinetics

In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, open-label, two-treatment, two-way, four-period, single-dose, crossover study comparing the pharmacokinetics of the test product Synetra 75 mg film-coated tablet (Alkaloid AD) and the reference product Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) in healthy adult male and female subjects under fasting conditions.

During each of the four study periods, the subjects were given a single 75 mg dose of either the test (T) or the reference (R) product with 240 ml of water, after at least a 10 hour overnight fast. The subjects were randomised to one of the two dosing sequences: TRTR or RTRT. The duration of the study was 21 days screening and 20 days active phase. Blood samples were collected before and up to 48 hours (24 hours during periods 1 and 2, and 48 hours during periods 3 and 4) after each administration. The washout period between the treatment periods was 5 days. The pharmacokinetic results for clopidogrel are presented below:

<table>
<thead>
<tr>
<th>Parameters (units)</th>
<th>Synetra 75 mg (Test)</th>
<th>Plavix 75 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td>AUC_{0-t} (pg h/mL)</td>
<td>1342.5±1269.1</td>
<td>1279.2±1123.0</td>
<td>104.50</td>
<td>96.70-112.92</td>
</tr>
<tr>
<td>AUC_{0-inf} (pg h/mL)</td>
<td>1446.3±1329.7</td>
<td>1372.7±1177.9</td>
<td>105.06</td>
<td>97.36-113.36</td>
</tr>
<tr>
<td>C_{max} (pg/mL)</td>
<td>1077.0±1237.7</td>
<td>1073.2±1316.1</td>
<td>106.95</td>
<td>98.08-116.61</td>
</tr>
</tbody>
</table>

AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
SD= standard deviation
Ratios and 90% geometric CI calculated from ln-transformed data

The Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits for the test/reference ratio for acceptance of bioequivalence as 80.00 % to 125.00 % for AUC and C_{max} values. The 90% confidence intervals of the test/reference ratio for AUC_{0-t}, AUC_{0-inf} and C_{max} lie within the acceptable limits. Thus, the data support the claim that the test product is bioequivalent to the reference product.

Efficacy

The efficacy of clopidogrel bisulphate is well-known. No new efficacy data have been submitted and none are required for an application of this type.
Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues were raised by the bioequivalence data.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and is in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Clopez 75 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none were required for this type of application.

Bioequivalence has been demonstrated between the applicant’s Clopez 75 mg film-coated tablets and the reference product Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none were required for this type of application. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory, and consistent with those for the reference product, where appropriate, along with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clopidogrel bisulphate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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