Public Assessment Report

Decentralised Procedure

Clopidogrel 75mg Film-coated Tablets

Procedure No: UK/H/1933/001/DC

UK Licence No: PL 29831/0415

Wockhardt UK Limited
Lay Summary

On 01 September 2010, Cyprus, Germany, France, Ireland, Malta, Poland and the UK agreed to grant a Marketing Authorisation to Wockhardt UK Limited for the medicinal product Clopidogrel 75mg Film-coated Tablets (PL 29831/0415; UK/H/1933/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 01 October 2010. This is a prescription-only medicine (POM) 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 have experienced a heart attack, stroke or have a condition known as peripheral arterial disease.

Clopidogrel 75mg 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).

Clopidogrel 75mg Film-coated Tablets are taken 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).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Clopidogrel 75mg Film-coated Tablets outweigh the risks and a Marketing Authorisation was granted.
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## Module 1
### Information about the initial procedure

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<tr>
<td>Type of Application</td>
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<td>Active Substances</td>
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<tr>
<td>MA Holder</td>
<td>Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK</td>
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Module 2
Summary of Product Characteristics

Please note that the Summary of Product Characteristics below is the version for the product that would be marketed in the UK only. The indications listed therein may differ in other member states.

1 NAME OF THE MEDICINAL PRODUCT
Clopidogrel 75mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 75mg of clopidogrel (as clopidogrel hydrochloride).
Excipients: each tablet contains 5.25mg hydrogenated castor oil.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Pink, round, biconvex tablets with a bevelled edge, plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Clopidogrel is indicated 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.
For further information please refer to section 5.1.

4.2 Posology and method of administration
• Adults and elderly
Clopidogrel should be given as a single daily dose of 75mg with or without food.
• Pharmacogenetics
CYP2C19 poor metaboliser status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolisers has yet to be determined (see Section 5.1).

• Paediatric patients
The safety and efficacy of clopidogrel in children and adolescents have not yet been established.

• 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).

4.3 Contraindications
• Hypersensitivity to the active substance or to any of the excipients.
• Severe liver impairment.
• Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

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: Based on literature data, patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function (see section 5.2).

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 medicinal products that inhibit CYP2C19 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**
This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 **Interaction with other medicinal products and other forms of interaction**

**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).

**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 500mg 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
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 medicinal products that inhibit CYP2C19 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:** In a crossover clinical study, clopidogrel (300mg loading dose followed by 75mg/day) alone and with omeprazole (80mg at the same time as clopidogrel) were administered for five days. The exposure to the active metabolite of clopidogrel was decreased by 45% (Day 1) and 40% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) with 5 µM ADP was diminished by 39% (24 hours) and 21% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole 12 hours apart did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Esomeprazole is expected to give a similar interaction with clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged (see section 4.4). No conclusive data on the pharmacodynamic interaction of clopidogrel and other PPIs are available.

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 studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P450 2C9. This could potentially lead to increased plasma levels of medicinal products such as phenytoin and tolbutamide and the NSAIDs, which are
metabolised by Cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

Apart from the specific 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 Pregnancy and lactation
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).

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel 75mg film-coated tablets.

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 42,000 patients who have participated in clinical studies, including over 9,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY and COMMIT studies are discussed below.

Overall, clopidogrel 75mg/day was comparable to ASA 325mg/day in CAPRIE regardless of age, gender and race. 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 1.4% for clopidogrel and 1.6% for ASA.

In CURE, the major bleeding event rate for clopidogrel+ASA was dose-dependent on ASA (<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo+ASA (<100mg: 2.0%; 100-200mg: 2.3%; >200mg: 4.0%). The risk of bleeding (life-threatening, major, minor, other) decreased during the course of the trial: 0-1 months (clopidogrel: 9.6%; placebo: 6.6%), 1-3 months (clopidogrel: 4.5%; placebo: 2.3%), 3-6 months (clopidogrel: 3.8%; placebo: 1.6%), 6-9 months (clopidogrel: 3.2%; placebo: 1.5%), 9-12 months (clopidogrel: 1.9%; placebo: 1.0%). There was no excess in major bleeds with clopidogrel + ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel+ASA vs. 5.3% placebo+ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel+ASA, and 6.3% for placebo+ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel + ASA group (17.4%) vs. the placebo + ASA group (12.9%). The incidence of major bleeding was similar between groups (1.3% versus 1.1% for the clopidogrel + ASA and the placebo + ASA groups, respectively). 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 (0.6% versus 0.5% in the clopidogrel + ASA and the placebo + ASA groups, respectively).

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>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Serum sickness, anaphylactoid reactions</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Hallucinations, confusion</td>
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<tr>
<td>Nervous system disorders</td>
<td>Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness</td>
<td></td>
<td>Taste disturbances</td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td>Eye bleeding (conjunctival, ocular, retinal)</td>
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<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td>Vertigo</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td>Haematoma</td>
<td></td>
<td>Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis</td>
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<td>Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis</td>
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<td>Gastrointestinal disorders</td>
<td>Gastrointestinal haemorrhage, diarrhoea, abdominal pain, abdominal pain, dyspepsia</td>
<td>Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence</td>
<td>Retroperitoneal haemorrhage</td>
<td>Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis</td>
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<td>Hepato-biliary disorders</td>
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<td>Acute liver failure, hepatitis, abnormal liver function test</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>Rash, pruritus, skin bleeding (purpura)</td>
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<td>Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme), angioedema, rash erythematous,</td>
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<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
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<tr>
<td>Musculoskeletal connective tissue and bone disorders</td>
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<td>urticaria, eczema, lichen planus</td>
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<td>Renal and urinary disorders</td>
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<td>Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia</td>
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<td>Investigations</td>
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</tbody>
</table>

### 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: B01AC-04.*

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 drugs, not all patients will have adequate platelet inhibition.

Repeated doses of 75mg 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 75mg 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 4 double-blind studies involving over 80,000 patients: the CAPRIE study, a comparison of clopidogrel to ASA, and the CURE, CLARITY and COMMIT 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 75mg/day or ASA 325mg/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.

5.2 Pharmacokinetic properties

Absorption

After single and repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5ng/ml after a single 75mg 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 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 the formation of the active metabolite, a thiol derivative of clopidogrel. In vitro, the metabolic pathway is mediated by CYP3A4, CYP2C19, CYP 1A2 and CYP2B6. The active thiol metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

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 75mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

Pharmacogenetics

Several polymorphic CYP450 enzymes activate clopidogrel. 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*9 and CYP2C19*3 alleles correspond to reduced metabolism. The CYP2C19*2 and CYP2C19*3 alleles account for 85% of reduced function alleles in whites and 99% in Asians. Other alleles associated with reduced metabolism include CYP2C19*4, *5, *6, *7, and *8, but these are less frequent in the general population. Published frequencies for the common CYP2C19 phenotypes and genotypes are listed in the table below.
To date, the impact of CYP2C19 genotype on the pharmacokinetics of the active metabolite of clopidogrel has been evaluated in 227 subjects from 7 reported studies. Reduced CYP2C19 metabolism in intermediate and poor metabolisers decreased the C\textsubscript{max} and AUC of the active metabolite by 30 – 50% following 300- or 600 – mg loading doses and 75 – mg maintenance doses. Lower active metabolite exposure results in less platelet inhibition or higher residual platelet reactivity. To date, diminished antiplatelet responses to clopidogrel have been described for intermediate and poor metabolisers in 21 reported studies involving 4,520 subjects. The relative difference in antiplatelet response between genotype groups varies across studies depending on the method used to evaluate response, but is typically greater than 30%.

The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post hoc clinical trial analyses (substudies of CLARITY [n=465] and TRITON – TIMI 38 [n=1,477]) and 5 cohort studies (total n=6,489). In CLARITY and one of the cohort studies (n=765; Trenk), cardiovascular event rates did not differ significantly by genotype. In TRITON – TIMI 38 and 3 of the cohort studies (n= 3,516; Collet, Sibbing, Giusti), patients with an impaired metaboliser status (intermediate and poor combined) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers. In the fifth cohort study (n=2,208; Simon), the increased event rate was observed only in poor metabolisers.

Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity.

There may be genetic variants of other CYP450 enzymes with effects on the ability to form the active metabolite of clopidogrel.

**Special populations**

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

**Renal impairment**

After repeated doses of 75mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/ml), 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 75mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

**Hepatic impairment**

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

**Race**

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

### 5.3 Preclinical safety data

During non clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.
At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

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

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

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Core:**
- Macrogol 6000
- Microcrystalline cellulose
- Low substituted hydroxypropylcellulose
- Glycerol dibehenate
- Castor oil hydrogenated

**Coat:**
- Opadry II, pink, containing:
  - Iron oxide red (E172),
  - Macrogol 4000
  - Poly (vinyl alcohol)
  - Titanium dioxide (E171)
  - Talc

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life

2 years.

#### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

#### 6.5 Nature and contents of container

Blisters strips (PVC/Aclar base or aluminium base with aluminium lid) contained in a cardboard box.

Pack size of 28, 50 and 84 film-coated tablets.

*Not all pack sizes may be marketed.*

#### 6.6 Special precautions for disposal

No special instructions.

Any unused product or waste material should be disposed of in accordance with local requirements.

### 7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd
Ash Road North
Wrexham
LL13 9UF
UK

### 8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0415
Module 3

Please note that the Patient Information Leaflet below is the version for the product that would be marketed in the UK only. The indications listed therein may differ in other member states.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clopidogrel 75mg film-coated Tablets
Clopidogrel (as hydrochloride)

Read all of this leaflet carefully before you start to take this medicine.
- Keep this leaflet. You may need to read it again while you are receiving treatment.
- 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. It may harm them, 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 Clopidogrel Tablets are and what they are used for
2. Before you take Clopidogrel Tablets
3. How to take Clopidogrel Tablets
4. Possible side effects
5. How to store Clopidogrel Tablets
6. Further information

1. WHAT CLOPIDOGREL TABLETS ARE AND WHAT THEY ARE USED FOR

Clopidogrel Tablets belong to a group of medicines called antiplatelet medicinal products. Platelets are very small structures in the blood, 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).

Clopidogrel Tablets are taken 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).

You have been prescribed Clopidogrel Tablets to help prevent blood clots and reduce the risk of these severe events because:
- You have a condition of hardening of the arteries (also known as atherosclerosis), and
- You have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease.

2. BEFORE YOU TAKE CLOPIDOGREL TABLETS

Do not take Clopidogrel Tablets:
- If you are allergic (hypersensitive) to clopidogrel or any of the other ingredients in Clopidogrel Tablets
- If you have a medical condition that is currently causing bleeding such as a stomach ulcer or bleeding within the brain
• If you suffer from severe liver disease

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

**Take special care with Clopidogrel Tablets:**

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

- if you have a risk of bleeding such as:
  - a medical condition that puts you at risk of internal bleeding (such as a stomach ulcer)
  - a blood disorder that makes you prone to internal bleeding (bleeding inside any tissues, organs or joints of your body)
  - a recent serious injury
  - a recent surgery (including dental)
  - a planned surgery (including dental) in the next seven days
- if you have had a clot in an artery of your brain (ischaemic stroke) which occurred within the last seven days
- if you have kidney or liver disease.

While you are taking Clopidogrel Tablets:

- You should tell your doctor if a surgery (including dental) is planned
- You should also tell your doctor immediately if you develop a medical condition (also known as Thrombotic Thrombocytopenic Purpura or TTP) that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see section 4 ‘Possible Side Effects’)
- If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 4 ‘Possible Side Effects’)
- Your doctor may order blood tests

Clopidogrel Tablets are not intended 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 influence the use of Clopidogrel Tablets or vice versa.

You should specifically tell your doctor if you take
- oral anticoagulants, medicines used to prevent blood clotting
- a non-steroidal anti-inflammatory medicine, usually used to treat painful and/or inflammatory conditions of muscle or joints
- heparin or any other medicine used to reduce blood clotting
- a proton pump inhibitor (e.g. omeprazole) for upset stomach
- fluconazole, voriconazole, ciprofloxacin, or chloramphenicol, medicines used to treat bacterial and fungal infections
- cimetidine, medicine to treat upset stomach
- fluoxetine, fluvoxamine, or moclobemide, medicines to treat depression
- carbamazepine, or oxcarbazepine, medicines to treat some forms of epilepsy
- ticlopidine, other antiplatelet agent.

**Taking Clopidogrel Tablets with food and drink**
Clopidogrel Tablets may be taken with or without food.

**Pregnancy and breast-feeding**
It is preferable not to use this product during pregnancy and breast-feeding.

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

While taking Clopidogrel Tablets, consult your doctor about the breast-feeding of a baby.

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

**Driving and using machines**
Clopidogrel Tablets are unlikely to affect your ability to drive or to use machines.

**Important information about some of the ingredients in Clopidogrel Tablets**
This medicine contains hydrogenated castor oil, which can cause stomach upsets and diarrhoea.

**3. HOW TO TAKE CLOPIDOGREL TABLETS**
Always take Clopidogrel Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one 75mg tablet of Clopidogrel per day to be taken orally with or without food, and at the same time each day.

You should take Clopidogrel Tablets for as long as your doctor continues to prescribe them.

**If you take more Clopidogrel Tablets than you should**
Contact your doctor or nearest hospital casualty department because of the increase risk of bleeding.

**If you forget to take Clopidogrel Tablets**
If you forget to take a dose of Clopidogrel Tablets, but remember within 12 hours of your usual time, take your tablet straight away and then take your next tablet at the usual time.

If you forget for more than 12 hours, simply take the next single dose at the usual time. Do not take a double dose to make up for the forgotten individual doses.

**If you stop taking Clopidogrel Tablets**
Do not stop the treatment. 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, Clopidogrel Tablets can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience:
- fever, signs of infection or extreme tiredness. These may be due to rare decrease of some blood cells
- signs of liver problems such as yellowing of the skin and/or the eyes (jaundice), whether or not associated with bleeding which appears under the skin as red pinpoint dots and/or confusion (see section 2 ‘Take special care with Clopidogrel Tablets’)
- swelling in the mouth or skin disorders such as rashes and itching, blisters of the skin. These may be the signs of an allergic reaction.

The most common side effect (affects 1 in 10 patients in 100) reported with Clopidogrel Tablets is bleeding. Bleeding may occur as bleeding in the stomach or bowels, bruising, haematoma (unusual bleeding or bruising under the skin), nose bleed, blood in the urine. In a small number of cases, bleeding in the eye, inside the head, the lung or the joints has also been reported.

If you experience prolonged bleeding when taking Clopidogrel Tablets
If you cut or injure yourself, it may take longer than usual for bleeding to stop. This is linked to the way your medicine works as it prevents the ability of blood clots to form. For minor cuts and injuries e.g., cutting yourself shaving, this is usually of no concern. However, if you are concerned by your bleeding, you should contact your doctor straightaway (see section 2 ‘Take special care with Clopidogrel Tablets).

Other side effects reported with Clopidogrel Tablets are:
Common side effects (affects 1 to 10 patients in 100): Diarrhoea, abdominal pain, indigestion or heartburn.

Uncommon side effects (affects 1 to 10 patients in 1,000); Headache, stomach ulcer, vomiting, nausea, constipation, excessive gas in stomach or intestines, rashes, itching, dizziness, abnormal touch sensation.

Rare side effects (affects 1 to 10 patients in 10,000): Vertigo.

Very rare side effects (affects less than 1 patient in 10,000): jaundice; severe abdominal pain with or without back pain; fever, breathing difficulties sometimes associated with cough; generalised allergic reactions; swelling in the mouth; blisters of the skin; skin allergy; inflammation of the mouth (stomatitis); decrease in blood pressure; confusion; hallucinations; joint pain; muscular pain; changes in the way things taste.

In addition, your doctor may identify changes in your blood or urine test results.
If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CLOPIDOGREL TABLETS

Keep out of the reach and sight of children.
This medicine does not require any special storage conditions.
Clopidogrel Tablets should not be taken after the expiry date on the label; the expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Clopidogrel Tablets contain
The active ingredient is clopidogrel. Each tablet contains 75mg of clopidogrel (as hydrochloride).

The other ingredients are: macrogol 6000, microcrystalline cellulose, low substituted hydroxypropyl cellulose, glycerol dibehenate, and castor oil hydrogenated in the tablet core and opadry II (containing iron oxide red (E172), macrogol 4000, polyvinyl alcohol, titanium dioxide (E171) and talc) in the tablet coating.

What Clopidogrel Tablets look like and the contents of the pack
Clopidogrel Tablets are round, pink tablets with bevelled edges. They are supplied in blister strips in a cardboard outer container in pack sizes of 28, 50 and 84 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Wockhardt UK Ltd,
Ash Road North,
Wrexham,
LL13 9UF, UK.

Manufacturer:
CP Pharmaceuticals Ltd,
Ash Road North,
Wrexham,
LL13 9UF, UK.

This medicinal product is authorised in the Member States of the EEA under the following names:
UK: Clopidogrel 75mg Film-Coated Tablets
Ireland: Clopidogrel 75mg Film-Coated Tablets
Germany: Clopidogrel 75mg Filmtabletten
Poland: Clopidogrel 75mg Tabletki Powlekane
Cyprus: Clopidogrel 75mg Film-Coated Tablets
Malta: Clopidogrel 75mg Film-Coated Tablets
France: Clopidogrel 75mg comprimé pelliculé

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000 (UK Only).

Please be ready to give the following information:

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Reference Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 75mg Tablets</td>
<td>PL 29831/0415</td>
</tr>
</tbody>
</table>
# Module 4
## Labelling

### PARTICULARS TO APPEAR ON THE OUTER CARTON

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel 75 mg Film-coated Tablets</td>
</tr>
<tr>
<td>2.</td>
<td>STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td></td>
<td>Each tablet contains 75 mg of clopidogrel (as clopidogrel hydrochloride)</td>
</tr>
<tr>
<td>3.</td>
<td>LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td></td>
<td>Contains hydrogenated castor oil. Read the package leaflet for further information.</td>
</tr>
<tr>
<td>4.</td>
<td>PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td></td>
<td>28 film-coated tablets</td>
</tr>
<tr>
<td></td>
<td>50 film-coated tablets</td>
</tr>
<tr>
<td></td>
<td>84 film-coated tablets</td>
</tr>
<tr>
<td>5.</td>
<td>METHOD AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td></td>
<td>For oral use</td>
</tr>
<tr>
<td></td>
<td>Read the package leaflet before use</td>
</tr>
<tr>
<td>6.</td>
<td>SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td></td>
<td>Keep out of the reach and sight of children</td>
</tr>
<tr>
<td>7.</td>
<td>OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>8.</td>
<td>EXPIRY DATE</td>
</tr>
<tr>
<td></td>
<td>(overprinted)</td>
</tr>
<tr>
<td>9.</td>
<td>SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td></td>
<td>No special storage conditions</td>
</tr>
<tr>
<td>10.</td>
<td>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td>11.</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td></td>
<td>Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham LL13 9UF, UK.</td>
</tr>
</tbody>
</table>
12. MARKETING AUTHORISATION NUMBER(S)

PL 29831/0415
PA 1339/26/1
MA 154/05401

13. BATCH NUMBER

(overprinted)

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Dose: As directed by your doctor

16. INFORMATION IN BRAILLE

Braille area (to appear under product name (number 1), on front face of carton only):
Clopidogrel 75 mg Film-coated Tablets

Other:
Affix dispensing label here
Wockhardt UK Ltd logo
### Minimum particulars to appear on blisters or strips

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>Name of the medicinal product</strong></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel 75 mg Film-coated Tablets</td>
</tr>
<tr>
<td>2.</td>
<td><strong>Name of the marketing authorisation holder</strong></td>
</tr>
<tr>
<td></td>
<td>Wockhardt UK Ltd</td>
</tr>
<tr>
<td>3.</td>
<td><strong>Expiry date</strong> (overprinted)</td>
</tr>
<tr>
<td>4.</td>
<td><strong>Batch number</strong> (overprinted)</td>
</tr>
<tr>
<td>5.</td>
<td><strong>Other</strong></td>
</tr>
</tbody>
</table>
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 Clopidogrel 75mg Film-coated Tablets (PL 29831/0415; UK/H/1933/001/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.

For further information please refer to section 5.1 of the Summary of Product Characteristics.

This was an abridged complex application submitted by the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and the Cyprus, Germany, France, Ireland, Malta and Poland as Concerned Member States (CMS). It was submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of Plavix 75mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France), which was registered via the Centralised Procedure on 15 July 1998.

Clopidogrel 75mg Film-coated Tablets contain the active ingredient, clopidogrel (as clopidogrel hydrochloride). 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.

The Marketing Authorisation Holder has submitted a single-dose acute oral toxicity study carried out on male Wistar rats at different doses level (1500, 2000 and 2500 mg/kg/day), to compare safety profile of clopidogrel hydrochloride with clopidogrel hydrogen sulphate. The non-clinical study was carried out in accordance with Good Laboratory Practice (GLP). No further non-clinical studies were conducted, 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.

Two single-dose, bioequivalence studies (one fasting and one fed) were submitted to support this application, comparing the test product Clopidrogel 75mg Film-coated Tablets (Wockhart UK Ltd, UK) and the reference product Plavix 75mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP). With the exception of these, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an innovator 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.
The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 01 September 2010. After a subsequent national phase, the licence was granted in the UK on 01 October 2010.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Clopidogrel 75 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Clopidogrel hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Platelet aggregation inhibitors (excluding heparin): ATC code: BO1AC04</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>75mg film-coated tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1933/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Cyprus, Germany, France, Ireland Malta and Poland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0415</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd, Ash Road North, Wrexham, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Clopidogrel hydrochloride

Chemical names: (αS)-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4H)-acetic acid methyl ester hydrochloride

Structure:

\[
\begin{align*}
\text{O} & \quad \text{OCH}_3 \\
\text{HCl} \\
\end{align*}
\]

Molecular formula: \( C_{16}H_{16}ClNO_2 \cdot SHCl \)
Molecular Mass: 358.3 (Clopidogrel base 321.8)
Appearance: A white to off-white crystalline powder. Freely soluble in methanol.

At the time of the assessment of this application, clopidogrel hydrochloride was not the subject of a 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 macrogol 6000, microcrystalline cellulose, low-substituted hydroxypropylcellulose, glycerol dibehenate, castor oil hydrogenated (making up the tablet core), and Opadry II pink, (the tablet coating). Opadry II pink is made up of iron oxide red (E172), macrogol 4000, poly(vinyl alcohol), titanium dioxide (E171) and talc. Appropriate justification for the inclusion of each excipient have been provided.
With the exception of low-substituted hydroxypropylcellulose and Opadry II Pink, all excipients comply with their respective European Pharmacopoeia monograph. Low-substituted hydroxypropylcellulose is controlled to its National Formulary specification. Opadry II Pink is controlled to a suitable in-house specification, however, its components are controlled to their respective European Pharmacopoeia monographs (with the exception of iron oxide red, which is controlled to its National Formulary specification). Satisfactory certificates of analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to produce a stable and robust immediate-release formulation, equivalent to 75mg of clopidogrel base (as clopidogrel hydrochloride), that could be considered as generic medicinal product of Plavix 75mg 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 75mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated 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 blisters strips (polvinylchloride/Aclar base or aluminium base with aluminium lid). These are packed into cardboard cartons with patient information leaflets in pack sizes of 28, 50 and 84 film-coated tablets.

Not all pack sizes may be marketed. However, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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 2 years has been proposed with no special storage conditions.
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), Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

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 Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report 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
Clopidogrel is a widely used well-known substance. The pharmacodynamic, pharmacokinetic and toxicological properties are well-characterised. However, this application is for a product containing clopidogrel hydrochloride as the active substance, instead of clopidogrel hydrogen sulphate that is used in the innovator product. To support the use of clopidogrel hydrochloride, an additional study has been submitted to compare the safety profile of clopidogrel hydrochloride with that for clopidogrel hydrogen chloride. This was a single-dose acute oral toxicity study, carried out in-line with current Good Laboratory Practice (GLP) on male Wistar rats at different doses level (1500, 2000 and 2500 mg/kg/day). No increase in mortality was observed in rats dosed with clopidogrel hydrochloride compared to those dosed with clopidogrel hydrogen sulphate. Furthermore, similar clinical observations observed in the rats (such as adverse event occurrence and recovery profiles) showed that clopidogrel hydrochloride and clopidogrel hydrogen sulphate have a similar safety profile.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the pharmacology and toxicology of clopidogrel hydrogen sulphate. In addition, the non-clinical overview includes an adequate discussion comparing clopidogrel hydrochloride and clopidogrel hydrogen sulphate.

Suitable justification has been provided for non-submission of an environmental risk assessment.

The grant of a marketing authorisation is recommended.
### III.3 CLINICAL ASPECTS

**Pharmacokinetics**

In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence studies (one under fasting and the other under fed conditions):

#### Fasting study

A randomised, open-label, two-treatment, two-sequence, two-period, single-dose, crossover study comparing the pharmacokinetics of the test product Clopidrogel 75mg Film-coated Tablets (Wockhardt UK Ltd, UK) and the reference product Plavix 75mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) in healthy male subjects under fasting conditions.

The subjects were given a 75mg dose of clopidogrel after at least a 10-hour fast. Blood samples were collected before and up to 36 hours after each administration. The washout period between the two treatment arms was 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Anti log of least square mean</th>
<th>Ratio T/R (%)</th>
<th>90% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C_{max} (pg/mL)</strong></td>
<td>1030.7812</td>
<td>1125.6167</td>
<td>91.57</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>83.83-100.03</td>
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<tr>
<td><strong>AUC_{0-t} (pg.hr/mL)</strong></td>
<td>2412.4512</td>
<td>2479.1922</td>
<td>97.31</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>91.60-103.37</td>
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<tr>
<td><strong>AUC_{0-∞} (pg.hr/mL)</strong></td>
<td>2611.0831</td>
<td>2726.0075</td>
<td>95.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>90.22-101.69</td>
</tr>
</tbody>
</table>

**Summary of pharmacokinetic parameters (log-transformed) – Fasted Study**

AUC_{∞} 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

#### Fed Study

A randomised, open label, two-treatment, two-sequence, two-period, single-dose, crossover study comparing the pharmacokinetics of the test product Clopidrogel 75mg Film-coated Tablets (Wockhardt UK Ltd, UK) and the reference product Plavix 75mg film-coated tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) in healthy male subjects under fed conditions.

The subjects were given a 75mg dose of clopidogrel half an hour after a high fat meal. Blood samples were collected before and up to 36 hours after each administration. The washout period between the two treatment arms was 7 days. The pharmacokinetic results are presented below:
Summary of pharmacokinetic parameters (log-transformed) – Fed Study

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Anti log of least square mean</th>
<th>Ratio T/R (%</th>
<th>90% Confidence Intervals</th>
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<tbody>
<tr>
<td>C_{max} (pg/mL)</td>
<td>4555.7835</td>
<td>4523.8224</td>
<td>100.71</td>
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<tr>
<td>AUC_{0-t} (pg.hr/mL)</td>
<td>12940.6897</td>
<td>12733.1059</td>
<td>101.63</td>
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<tr>
<td>AUC_{0-∞} (pg.hr/mL)</td>
<td>13323.9061</td>
<td>12988.4714</td>
<td>102.58</td>
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</tbody>
</table>

AUC_{0-t}, area under the plasma concentration-time curve from time zero to t hours
AUC_{0-∞}, area under the plasma concentration-time curve from time zero to infinity
C_{max}, maximum plasma concentration

The results of both studies showed that the 90% Confidence Intervals for log-transformed AUC_{0-t}, AUC_{0-∞} and C_{max} were within the predefined acceptance criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). The data support the claim that the test product can be considered a generic medicinal product of the reference product.

Pharmacodynamics
No new pharmacodynamic data have been submitted for this application. As the pharmacodynamic profile of clopidogrel is already well-known through the clinical use of clopidogrel hydrogen sulphate, this is considered to be satisfactory.

Efficacy and Safety
No new efficacy data have been submitted for this application. As the efficacy of clopidogrel is already well-known through the clinical use of clopidogrel hydrogen sulphate, this is considered to be satisfactory.

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.

A suitable discussion has been provided concerning the efficacy and safety of clopidogrel hydrochloride and clopidogrel hydrogen sulphate. The discussion shows that clopidogrel can be considered to have the same efficacy in either salt formation

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are clinically acceptable. The SmPC is consistent with those for the innovator product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

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.

**Conclusion**
The grant of a marketing authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Clopidogrel 75mg 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
The pharmacodynamic, pharmacokinetic and toxicological properties of clopidogrel are well-characterised, albeit as clopidogrel hydrogen sulphate. As this product contains clopidogrel hydrochloride, additional data from a non-clinical study on rats was submitted. This study showed that the safety profiles of clopidogrel hydrochloride and clopidogrel hydrogen sulphate could be considered to be comparable. With the exception of this study, no new non-clinical data were submitted and none were required. The non-clinical expert report submitted provides an appropriate review of the non-clinical data for clopidogrel hydrochloride and a suitable discussion comparing this to the clopidogrel hydrochloride.

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

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

SAFETY
No new or unexpected safety concerns arise from this application. A suitable discussion has been provided concerning the safety of clopidogrel hydrochloride and clopidogrel hydrogen sulphate. The discussion shows that clopidogrel can be considered to have the same safety in either salt formulation.

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

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with clopidogrel is considered to have demonstrated the therapeutic value of the compound. The benefit/risk 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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