Public Assessment Report

Clopidogrel 75 mg film-coated tablets

(clopidogrel hydrogen sulfate)

UK Licence No.: PL 42930/0018

Wilcare Pharma Limited
Lay Summary
Clopidogrel 75 mg film-coated tablets
(clopidogrel hydrogen sulfate)

This is a summary of the Public Assessment Report (PAR) for Clopidogrel 75 mg film-coated tablets (PL 42930/0018). This medicinal product will be referred to as Clopidogrel Tablets in the remainder of the summary, for ease of reading.

This summary explains how Clopidogrel Tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Clopidogrel Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Clopidogrel Tablets and what are they used for?
This medicine is the same as Clopidogrel 75 mg film-coated tablets (PL 34771/0062), which is already authorised. The company that makes Clopidogrel 75 mg film-coated tablets (PL 34771/0062), Macleods Pharma UK Limited, has agreed that its scientific data can be used as a basis for the grant of an identical licence for Clopidogrel Tablets (PL 42930/0018).

Clopidogrel Tablets are taken by adults to prevent blood clots (thrombi) forming in hardened blood vessel (arteries), a process known as atherothrombosis, which can lead to atherothrombotic events (such as stroke, heart attack or death).

Clopidogrel Tablets are prescribed to help prevent blood clots and reduce the risk of these severe events because:

- Patients have a condition of hardening of arteries (also known as atherosclerosis), and
- Patients have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease, or
- Patients have experienced a severe type of chest pain known as ‘unstable angina’ or ‘myocardial infarction’ (heart attack). For the treatment of this condition a doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. Patients 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 a doctor.
- Patients have an irregular heartbeat, a condition called ‘atrial fibrillation’, and patients cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. Patients should have been told that ‘oral anticoagulants’ are more effective than acetylsalicylic acid or the combined use of Clopidogrel Tablets and acetylsalicylic acid for this condition. A doctor should have prescribed Clopidogrel Tablets plus acetylsalicylic acid if patients cannot take oral anticoagulants’ and they do not have a risk of major bleeding.
How do Clopidogrel Tablets work?
Clopidogrel Tablets contain the active substance clopidogrel hydrogen sulfate, which 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 clots forming (a process called thrombosis).

How are Clopidogrel Tablets used?
Clopidogrel Tablets are taken by mouth.

The recommended dose, including for patients with a condition called ‘atrial fibrillation’ (an irregular heartbeat), is one 75 mg of Clopidogrel Tablets per day with or without food, and at the same time each day.

Patients who have experienced severe chest pain (unstable angina or heart attack), a doctor may give them 300 mg of Clopidogrel Tablets (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one Clopidogrel 75 mg Tablets per day as described above.

Clopidogrel Tablets can only be obtained with a prescription from a doctor.

For further information on how Clopidogrel Tablets are used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Clopidogrel Tablets have been shown in studies?
As Clopidogrel Tablets (PL 42930/0018) is considered to be identical to Clopidogrel 75 mg film-coated tablets (PL 34771/0062), its benefits and risks are taken as being the same as those for Clopidogrel 75 mg film-coated tablets (PL 34771/0062).

What are the possible side effects from Clopidogrel Tablets?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effect with Clopidogrel Tablets which may affect more than 1 in 10 people 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.

The common side effects with Clopidogrel Tablets which may affect up to 1 in 10 people are diarrhoea, abdominal pain, indigestion or heartburn.

For the full list of all side effects reported with Clopidogrel Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.
Why are Clopidogrel Tablets approved?
No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Clopidogrel Tablets outweigh the risks, and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Clopidogrel Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Clopidogrel Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Clopidogrel Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Clopidogrel Tablets
A Marketing Authorisation was granted in the UK on 27 June 2016.

For more information about taking Clopidogrel Tablets, read the package leaflet, or contact your doctor or pharmacist.

The full PAR for Clopidogrel Tablets follows this summary.

This summary was last updated in August 2016.
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I Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Wilcare Pharma Limited a Marketing Authorisation for the medicinal product Clopidogrel 75 mg film-coated tablets (PL 42930/0018) on 27 June 2016. This product is a prescription only medicine (POM) indicated in:

Prevention of atherothrombotic events 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.

This application was submitted as abridged simple application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Clopidogrel 75 mg film-coated tablets, which was first authorised to Macleods Pharma UK Limited (PL 34771/0062) on 09 October 2012.

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.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross-reference product.
The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application, and these are satisfactory.
II  Quality aspects

II.1  Introduction
This is an abridged simple, piggyback (informed consent) application for Clopidogrel 75 mg film-coated tablets (PL 42930/0018), submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Clopidogrel 75 mg film-coated tablets, which was first authorised to Macleods Pharma UK Limited (PL 34771/0062) on 09 October 2012. The current application is considered valid.

II.2  Drug Substance
Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3  Medicinal Product
Name
The proposed product name is Clopidogrel 75 mg film-coated tablets. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size
Each film-coated tablet contains 75 mg clopidogrel (as clopidogrel hydrogen sulfate), as active ingredient. The route of administration is oral.

The finished product is packed into oriented polyamide (OPA) / poluvinychloride (PVC) and aluminium foil blisters in a cartons box with a pack size of 28 tablets.

The proposed shelf-life is 3 years with no special storage conditions.

The proposed packaging and shelf-life are consistent with the details registered for the cross-reference product.

Legal status
This product is a prescription only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Wilcare Pharma Limited, Building 6 Unit 14, Croxley, Green Business Park, Watford, England WD18 8YH

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory Curriculum Vitae (CV) has been provided.

Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.
Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

Bioequivalence
No bioequivalence data are required to support this simple abridged application as the proposed product is manufactured to the same formula utilising the same process as the cross-reference product, Clopidogrel 75 mg film-coated tablets (PL 34771/0062).

Expert Report
The applicant cross-refer to the data for Clopidogrel 75 mg film-coated tablets (PL 34771/0062), to which this application is claimed to be identical. This is acceptable. The applicant has included expert reports of the application. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The quality data for this application is consistent with those approved for Clopidogrel 75 mg film-coated tablets (PL 34771/0062) and, as such, have been judged to be satisfactory. The grant of a Marketing Authorisation is recommended.

III Non-clinical aspects
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data has been supplied and none are required.

A suitable justification has been provided for not submitting an environmental risk assessment.

The grant of a Marketing Authorisation is recommended.

IV Clinical aspects
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The grant of a Marketing Authorisation is recommended.
Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clopidogrel 75 mg film-coated tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Haemorrhage, including major bleeding</td>
<td>The risks of haemorrhage, including major bleeding associated with the use of the drug product are adequately considered in the SPC Sections 4.3, 4.4, 4.8, and 4.9, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Haematological disorders including thrombocytopenia, leucopenia, neutropenia, agranulocytosis, acquired haemophilia etc.</td>
<td>The risks of haematological disorders including thrombocytopenia, leucopenia, neutropenia, agranulocytosis, acquired haemophilia etc. associated with the use of the drug product are adequately considered in the SPC Sections 4.4, 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
<td>The risks of TTP associated with the use of the drug product are adequately considered in the SPC Sections 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>Use in patients who are poor CYP2C19 metabolisers leading to reduced plasma levels of clopidogrel</td>
<td>The risks associated with the use of the drug product in patients who are poor CYP2C19 metabolisers leading to reduced plasma levels of clopidogrel are adequately considered in the SPC Section 4.4 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Risk of reduced plasma levels of clopidogrel due to interaction with strong or moderate CYP2C19 inhibitors</td>
<td>The risks of reduced plasma levels of clopidogrel due to interaction with strong or moderate CYP2C19 inhibitors associated with the use of the drug product are adequately considered in the SPC Sections 4.4. 4.5. and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Concomitant use of other medications that affect haemostasis</td>
<td>The risks associated with the concomitant use of the drug product with other medications that affect haemostasis are adequately considered in the SPC Section 4.5, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>The risks of eosinophilic pneumonia associated with the use of the drug product are adequately considered in the SPC Section 4.8 and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Cross-reactions (hypersensitivity) among thienopyridines (e.g. clopidogrel, ticlopidine, prasugrel)</td>
<td>The risks of cross-reactions (hypersensitivity) among thienopyridines (e.g. clopidogrel, ticlopidine, prasugrel) associated with the use of the drug product are adequately considered in the</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>Gastrointestinal disturbances</td>
<td>The risks of gastrointestinal disturbances associated with the use of the drug product are adequately considered in the SPC Sections 4.4, 4.8, and 5.3, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
</tr>
<tr>
<td>Use in children and adolescents – lack of efficacy</td>
<td>The risks associated with the use of the drug product in children and adolescents – lack of efficacy are adequately considered in the SPC Sections 4.2 and 5.1, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
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<td>Use in patients with recent (&lt;7 days) episode of ischemic stroke</td>
<td>As per the SPC Section 4.4 in view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.</td>
<td>None</td>
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<td>Use in patients with renal impairment</td>
<td>As per the SPC Sections 4.2, 4.4, and 5.2, therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in renally impaired patients.</td>
<td>None</td>
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<tr>
<td>Use in patients with hepatic impairment</td>
<td>As per the SPC Sections 4.2, 4.3, 4.4, and 5.2, therapeutic experience with clopidogrel is limited in patients with hepatic disease. Therefore, clopidogrel should be used with caution in patients with hepatic impairment and should not be used in patients with severe hepatic impairment.</td>
<td>None</td>
</tr>
<tr>
<td>Use in pregnancy and lactation</td>
<td>As per the SPC Sections 4.6 and 5.3, no clinical data on exposure to clopidogrel during pregnancy are available; therefore, it is</td>
<td>None</td>
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</tbody>
</table>
The applicant proposes only routine risk minimisation measures, which are detailed in the SmPC. These are considered sufficient. No additional risk minimisation measures are considered necessary.

V  User consultation
The package leaflet is identical to the leaflet for the reference product.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant’s product is identical to the reference product. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics, Patient Information Leaflet & Labels

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for this product are available on the MHRA website.

The current approved label is listed below:
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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