Public Assessment Report
Decentralised Procedure

Clopidogrel 75 mg Film-Coated Tablets

Clopidogrel hydrogen sulfate

UK/H/3564/001/DC

UK licence no: PL 34771/0062

Macleods Pharma UK Limited
LAY SUMMARY

On 9th October 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Macleods Pharma UK Limited for the medicinal product Clopidogrel 75 mg Film-coated Tablets (PL 34771/0062; UK/H/3564/001/DC). This medicine is only available on prescription from the doctor.

Clopidogrel Tablets 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).

Clopidogrel Tablets is 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).

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

- have a condition of hardening of arteries (also known as atherosclerosis), and
- have previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease, or
- 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 effectively blood flow. You 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 your doctor.
- have an irregular heartbeat, a condition called ‘atrial fibrillation’, and you cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. You 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. The doctor should have prescribed Clopidogrel Macleods plus acetylsalicylic acid if you cannot take ‘oral anticoagulants’ and do not have a risk of major bleeding.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Clopidogrel 75 mg Film-coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
# TABLE OF CONTENTS

Module 1: Information about initial procedure  Page 4  
Module 2: Summary of Product Characteristics  Page 5  
Module 3: Patient Information Leaflet  Page 6  
Module 4: Labelling  Page 7  
Module 5: Scientific Discussion  Page 9  
   
   I. Introduction  
   II. About the Product  
   III. Scientific Overview and Discussion  
      III.1. Quality aspects  
      III.2. Non-clinical aspects  
      III.3. Clinical aspects  
   IV. Overall conclusion and Benefit-Risk Assessment  
   
Module 6  Steps taken after initial procedure  Page 17
**Module 1**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Clopidogrel 75 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Clopidogrel hydrogen sulfate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>75 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Macleods Pharma UK Limited Crewe Hall, Crewe, Cheshire CW1 6UL, UK</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Germany, Italy and Spain</td>
</tr>
<tr>
<td><strong>Procedure Numbers</strong></td>
<td>UK/H/3564/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 26th September 2012</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

Foil artwork (14 Tablets)
Clopidogrel 75 mg film-coated tablets

Clopidogrel 75 mg film-coated tablets  clopidogrel  Macleods Pharma UK Limited

Space for Embossing Batch no. and Exp date instead of Space for batch details.

Colours: Black
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (United Kingdom) and Concerned Member States (Germany, Italy and Spain) consider that the application for Clopidogrel 75 mg Film-coated Tablets in the treatment of the following indications could be approved.

- 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 is for Clopidogrel 75 mg Film-coated Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended. The application cross refers to Plavix 75 mg Film-coated Tablets (EM 15713/0004), authorised to Sanofi Pharma Bristol-Myers Squibb SNC, France and registered via centralised procedure in the EU since 15th July 1998. The reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the RMS in this Decentralised Procedure (UK/H/3564/001/DC), Macleods Pharma UK Limited applied for the Marketing Authorisation for Clopidogrel 75 mg Film-coated Tablets in Germany, Italy and Spain.

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 non-clinical and clinical studies were conducted, which is acceptable given that the application was based on being a generic version of the originator product that has been
licensed for over 10 years. A bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS 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.

For manufacturing sites within and outside the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that 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. A suitable justification has been provided for non-submission of a Risk Management Plan.

All Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 26th September 2012). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on 9th October 2012 (PL34771/0062).
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 hydrogen sulfate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>B01AC-04.</td>
</tr>
<tr>
<td></td>
<td>Platelet aggregation inhibitors excl. heparin</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated Tablets, 75 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedures</td>
<td>UK/H/3564/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Germany, Italy and Spain</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 34771/0062</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Macleods Pharma UK Limited</td>
</tr>
<tr>
<td></td>
<td>Crewe Hall,</td>
</tr>
<tr>
<td></td>
<td>Crewe,</td>
</tr>
<tr>
<td></td>
<td>Cheshire</td>
</tr>
<tr>
<td></td>
<td>CW1 6UL, UK</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

DRUG SUBSTANCE
INN: Clopidogrel hydrogen sulfate

Chemical Name: Methyl (2S)-(2-chlorophenyl)[6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl]acetate sulfate

Structure:

![Structure of Clopidogrel](image)

Molecular Formula: C_{16}H_{16}ClNO_{2}S \cdot H_{2}SO_{4}
Molecular Weight: 419.90

Appearance: A white to off-white powder, freely soluble in methanol, practically insoluble in ether and water.

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug substance from the designated starting material 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.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, low substituted hydroxypropyl cellulose, silica colloidal anhydrous, castor oil hydrogenated, dimeticone making up the tablet core, and the film coat is consisted of hydroxypropylmethylcellulose 2910/Hypromellose (E464), macrogol 400,titanium dioxide (E171) and iron oxide red (E172). Appropriate justification for the inclusion of each excipient has been provided.
All excipients comply with their respective European Pharmacopoeia monographs with the exception of the low substituted hydroxypropyl cellulose that complies with National formulary and the film-coat (hydroxypropylmethyl cellulose 2910/Hypromellose (E464), macrogol 400, titanium dioxide (E171) and iron oxide red (E172)) which comply with an in-house specification. 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 the production of this product is sourced from healthy animals under the same conditions as that intended for human consumption.

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 robust, stable tablets that contain the same active ingredient as Plavix 75 mg film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

Comparative impurity and dissolution profiles have been presented for the test and reference products.

**Manufacture**

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 and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished Product Specification**

The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

The finished product is packed in OPA (Oriented polyamide)/aluminium/polyvinylechloride (PVC) and aluminium foil blisters, available in a pack of 28, tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with no special storage conditions is set. This is satisfactory.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

Marketing Authorisation Application (MAA) Forms
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
There are no objections to the approval of this product from a pharmaceutical point of view.

III.2  NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of clopidogrel hydrogen sulfate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

III.3  CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
To support this application, the Marketing Authorisation Holder submitted the following bioequivalence study:

Randomised, open label, two-period, two-treatment, two-sequence, single dose, crossover bioequivalence study of Clopidogrel Tablets 75 mg (Macleods Pharmaceuticals Ltd., India) and Plavix® Tablets 75 mg (Sanofi Pharma, BMS, France) in 60 healthy, adult, male subjects under fasting condition.

Blood samples were collected prior to study drug administration and at 0.167, 0.33, 0.50, 0.67, 0.83, 1.00, 1.167, 1.33, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.00, 12.00,
16.00, 20.00, 24.00 and 32.00 hours post-dose in each period. The wash-out period was 7 days between the treatments.

Results

Pharmacokinetic parameters: Clopidogrel (N = 58)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Least Square Mean</th>
<th>90% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-t}$ (ratio test/reference)</td>
<td>100.71</td>
<td>89.84 – 112.90</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ratio test/reference)</td>
<td>101.83</td>
<td>90.51 – 114.56</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ratio test/reference)</td>
<td>107.52</td>
<td>94.05 – 122.92</td>
</tr>
</tbody>
</table>

$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

$C_{\text{max}}$ maximum plasma concentration

The results show that the 90% confidence intervals for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ fell within the acceptable range (80-125%). Bioequivalence has been demonstrated between the test formulation (Clopidogrel Tablets 75 mg) and the reference formulation (Plavix® Tablets 75 mg).

Efficacy

No new efficacy data have been submitted and none are required for this application.

Safety

No new safety data have been submitted and none are required for this application.

Expert Report

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Summary of Product Characteristics

This is satisfactory.

Patient Information Leaflet

This is satisfactory.

Labelling

This is satisfactory.

MAA Form

This is satisfactory.

Conclusions

There are no objections to the approval of this product from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Clopidogrel 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 applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Clopidogrel Tablets 75 mg and the reference product, Plavix® Tablets 75 mg.

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with those of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT 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 hydrogen sulfate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>