Public Assessment Report

Decentralised Procedure

Clopidogrel 75 mg Film-coated Tablets

Procedure No: UK/H/1348/001/DC

UK Licence No: PL 20075/0111

Accord Healthcare Limited
Lay Summary

Clopidogrel 75 mg Film-coated Tablets (clopidogrel hydrogen sulphate)

This is a summary of the public assessment report (PAR) for Clopidogrel 75 mg Film-coated Tablets (PL 20075/0111; UK/H/1348/001/DC). It explains how Clopidogrel 75 mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Clopidogrel 75 mg Film-coated Tablets.

For practical information about using Clopidogrel 75 mg Film-coated Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Clopidogrel 75 mg Film-coated Tablets and what are they used for?
Clopidogrel 75 mg Film-coated Tablets are a generic medicine. This means that Clopidogrel 75 mg Film-coated Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Plavix 75 mg Film-coated Tablets.

Clopidogrel 75 mg Film-coated Tablets are taken by adults 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).

How do Clopidogrel 75 mg Film-coated Tablets work?
Clopidogrel 75 mg Film-coated Tablets contain the active substance clopidogrel (as clopidogrel hydrogen sulphate) and 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).

How are Clopidogrel 75 mg Film-coated Tablets used?
Clopidogrel 75 mg Film-coated Tablets should be taken as a single daily dose of 75 mg, orally, with or without food, at the same time each day. If the patient has experienced severe chest pain (unstable angina or heart attack), the prescribing doctor may give the patient 300 mg of clopidogrel (4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg of clopidogrel per day. Clopidogrel tablets should be taken for as long as the prescribing doctor continues to prescribe it.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Clopidogrel 75 mg Film-coated Tablets have been shown in studies?
Because Clopidogrel 75 mg Film-coated Tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Plavix 75 mg Film-coated Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the possible side effects of Clopidogrel 75 mg Film-coated Tablets?
Because Clopidogrel 75 mg Film-coated Tablets are a generic medicine and are bioequivalent to the reference medicine, their benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the PIL.

Why are Clopidogrel 75 mg Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Clopidogrel 75 mg Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to Plavix 75 mg Film-coated Tablets. Therefore, it was decided that, as for Plavix 75 mg Film-coated Tablets, the benefits are greater than their risks and it was recommended that Clopidogrel 75 mg Film-coated Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Clopidogrel 75 mg Film-coated Tablets?
Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Clopidogrel 75 mg Film-coated Tablets
Bulgaria, Czech Republic, Denmark, Estonia, Finland, Hungary, Lithuania, Latvia, Poland, Romania, Slovak Republic and the UK agreed to grant a marketing authorisation for Clopidogrel 75 mg Film-coated Tablets on 17 November 2010. The marketing authorisation in the UK was granted on 22 December 2010.

On 03 March 2013, following the completion of a repeat-use Mutual Recognition procedure, Austria, Cyprus, Germany, France, Ireland, Malta, the Netherlands, Norway and Sweden also agreed to grant the marketing authorisation for Clopidogrel 75 mg Film-coated Tablets.

The full PAR for Clopidogrel 75 mg Film-coated Tablets follows this summary.

For more information about treatment with Clopidogrel 75 mg Film-coated Tablets, read the PIL or contact your doctor or pharmacist.

This summary was last updated in December 2014.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Clopidogrel 75 mg Film-coated Tablets (PL 20075/0111; UK/H/1348/001/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.

This was an abridged complex application submitted by the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Bulgaria, Czech Republic, Denmark, Estonia, Finland, Hungary, Lithuania, Latvia, Poland, Romania and Slovak Republic 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 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France), which was registered via the Centralised Procedure on 15 July 1998.

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

One single-dose, bioequivalence study was submitted to support this application, comparing the test product Clopidogrel 75 mg Film-coated Tablets (Accord Healthcare Limited, UK) versus the reference product Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP). With the exception of this bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

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

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 17 November 2010. After a subsequent national phase, the licence was granted in the UK on 22 December 2010.

After the grant of the initial procedure, the marketing authorisation for the reference medicinal product underwent a change in ownership, on 18 April 2012, to the current marketing authorisation holder, Sanofi Clir SNC.
II Quality aspects

II.1 Introduction
The product is a pink coloured, round, biconvex, film-coated tablet, plain on both sides.

Each tablet contains 75 mg of the active substance clopidogrel (as hydrogen sulphate). The excipients present in the core are anhydrous lactose, low-substituted hydroxypropyl cellulose, hydroxy propyl cellulose, cellulose, microcrystalline (PH 112)(E460), hydrogenated castor oil and colloidal anhydrous silica (E551). The excipients present in the coating are hydroxy propyl cellulose, triacetin (E1518), iron oxide red (E172), hypromellose (E464), titanium dioxide (E171) and lactose monohydrate.

The tablets are presented in aluminium/aluminium blisters, which are further packed into cartons in pack sizes of 7, 14, 28, 30, 50, 84, 90 and 100 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 (Directive 2002/72/EC, as amended) concerning materials in contact with foodstuff.

II.2 Drug Substance
Clopidogrel hydrogen sulphate

INN: Clopidogrel hydrogen sulphate
Chemical names: Methyl (+)-(S)-α-(o-chlorophenyl)-6,7-dihydrothieno [3,2-c] pyridine-5(4H)-acetate, sulfate (1 :1);
(αS)- α-(2-Chlorophenyl) 6,7-dihydrothieno [3,2-c] pyridine-5 (4H)-acetic acid methyl ester, hydrogen sulfate
(+)-Methyl-α-5-[4,5,6,7-tetrahydro [3,2-c] thienopyridyl]-(2-chlorophenyl) acetate, hydrogen sulphate

Structure:

\[
\text{Molecular formula: } C_{16}H_{16}ClNO_{2}S \cdot H_{2}SO_{4} \\
\text{Molecular mass: } 419.90 \\
\text{Appearance: } \text{A white to off-white crystalline powder. Soluble in methanol and practically insoluble in ether.}
\]

At the time of the assessment of this application, clopidogrel hydrogen sulphate 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.

II.3 Medicinal Product
Pharmaceutical development
The objective of the development programme was to produce a stable and robust formulation of Clopidogrel 75 mg Film-coated Tablets that could be considered a generic medicinal product of Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France).

Suitable pharmaceutical development data have been provided for this application.

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

In order to show that Clopidogrel 75 mg Film-coated Tablets are equivalent to the reference product, Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France), with regard to bioavailability, a bioequivalence study was performed. This is discussed in Section IV – Clinical aspects. Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of low substituted hydroxypropylcellulose and iron oxide red (E172), all excipients comply with their respective European Pharmacopoeia monograph. Low-substituted hydroxypropylcellulose and iron oxide red (E172) are controlled to their respective National Formulary specifications. In addition, the specification for iron oxide red (E172) is in compliance with Directive 78/25/EC (concerning use of colouring agents in foodstuff). Satisfactory certificates of analysis have been provided for all excipients.

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

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

Stability of the Product
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with no special storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects
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. The grant of a marketing authorisation is recommended.

III Non-clinical aspects
As the pharmacodynamic, pharmacokinetic and toxicological properties of clopidogrel hydrogen sulphate are well-known, no further non-clinical studies are required and none have been provided.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution of products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

Conclusion
The grant of a marketing authorisation is recommended.

IV Clinical aspects
IV.1 Introduction
With the exception of bioequivalence data, no new clinical data have been submitted and none are required for this type of application. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:
A randomised, open-label, two-treatment, two-sequence, two-period, single-dose, crossover study comparing the pharmacokinetics of the test product Clopidrogel 75 mg Film-coated Tablets (Accord Healthcare Limited, UK) and the reference product Plavix 75 mg Film-coated Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) in healthy adult male subjects under fasting conditions.

The subjects were given a 75 mg 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 8 days. The pharmacokinetic results are presented below:

| Pharmacokinetic parameters (geometric mean, ratio and confidence intervals [CI]) of Clopidogrel |
|-------------------------------------------------|-------------------------------------------------|-----------------|-----------------|
| Parameters (units)                              | Clopidogrel 75 mg (Test)                        | Plavix 75 mg (Reference) | Test/Ref Ratio (%) | 90% CI |
| AUC\(_{0-t}\) (ng h/mL)                        | 1639.160                                        | 1727.669                   | 94.9             | 85.21-105.64 |
| AUC\(_{0-\infty}\) (ng.h/mL)                   | 1753.252                                        | 1841.668                   | 95.2             | 85.74-105.70 |
| C\(_{\text{max}}\) (ng/mL)                     | 808.899                                         | 847.344                    | 95.5             | 84.82-107.44 |

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

Ratios and 90% geometric CI calculated from ln-transformed data

The 90% confidence intervals of the test/reference ratio of geometric means for AUC\(_{0-t}\), AUC\(_{0-\infty}\) and C\(_{\text{max}}\) lie within the acceptable limits (80% to 125%). Thus, the data support the claim that the test product is bioequivalent to the reference product.

IV.3 Pharmacodynamics
The pharmacodynamics of clopidogrel hydrogen sulphate are well-known. No new pharmacodynamic data are provided or required for this application.

IV.4 Clinical efficacy
The efficacy of clopidogrel hydrogen sulphate is well-known. No new efficacy data have been submitted and none are required for an application of this type.

IV.5 Clinical safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Risk Management Plan (RMP)
Suitable justification has been provided for not submitting a risk management plan for this product.

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.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.
V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clopidogrel hydrogen sulphate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Annex 1 - Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL)

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.
Annex 2 – Product labelling approved during the initial procedure
Annex 3 - Table of content of the PAR update for MRP and DCP

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

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
<tbody>
<tr>
<td>To update the SmPC in line with the Innovator SmPC following a repeat-use procedure.</td>
<td>UK/H/1348/001/IB/005</td>
<td>Y</td>
<td>26 Nov 2013</td>
<td>17 Jan 2014</td>
<td>Approval</td>
<td>Y</td>
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<tr>
<td>To submit a new bio-equivalence study, as per the commitment made during the repeat-use procedure.</td>
<td>UK/H/1348/001/II/009</td>
<td>N</td>
<td>26 Jun 2014</td>
<td>03 Nov 2014</td>
<td>Approval</td>
<td>Y</td>
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Annex 4 - Assessment reports of post-authorisation procedures affecting the PAR and updated product labelling

Assessment report for UK/H/1348/001/IB/005

Reference: PL 20075/0111 – 0015; UK/H/1348/001/IB/005
Product: Clopidogrel 75 mg Film-coated Tablets
Marketing Authorisation Holder: Accord Healthcare Limited
Active Ingredient: Clopidogrel hydrogen sulphate

Scope:
To update sections 2, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2, 6.1, 6.5 and 6.6 of the SmPC in-line with the Innovator SmPC (Plavix 75 mg film-coated tablets) of Sanofi Pharma Bristol-Myers Squibb SNC following a repeat-use procedure (UK/H/1348/001/E/001). Consequently, the label and PIL have been updated.

Supporting Evidence:
A revised Label, Patient Information Leaflet (PIL) and Summary of Product Characteristics (SmPC) have been provided.

Evaluation:
The amended sections of the SmPC, the amended label and PIL are all satisfactory.

The current approved UK versions of the SmPC and PIL for this product are available on the MHRA website. The approved product labelling resulting from this update is presented below.

Decision - Granted
Date 17/01/2014
Updated product labelling for UK/H/1348/001/IB/005
Updated product labelling for UK/H/1348/001/IB/005
Updated product labelling for UK/H/1348/001/IB/005
Assessment report for UK/H/1348/001/II/009

Reference: PL 20075/0111 – 0020; UK/H/1348/001/II/009.
Product: Clopidogrel 75 mg Film-coated Tablets
Marketing Authorisation Holder: Accord Healthcare Limited
Active Ingredient: Clopidogrel hydrogen sulphate

Reason:
To submit a new bioequivalence study as per the commitment made during repeat-use procedure UK/H/1348/001/E/001. No changes to product information apply.

Supporting Evidence
A new bioequivalence study was submitted.

The study was a randomized, open-label, 2-way crossover bioequivalence study to compare the bioequivalence of the test product, Clopidogrel 75 mg Film-Coated Tablets, with the reference product, Plavix 75 mg Film-coated tablets, following a 75 mg single dose in healthy subjects under fasting conditions.

Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 16 hours post dose. The two treatment periods were separated by a 6 day washout period. A total of 80 healthy adult subjects were enrolled and randomised, however, five subjects did not participate in period 2, so the pharmacokinetic analysis population was 75 subjects. The reasons for withdrawal/discontinuation from the study have been given and are acceptable.

The main pharmacokinetic results are presented below:

Bioequivalence results for ln-transformed test/reference ratios with 90% Confidence Intervals

<table>
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<th>Parameters</th>
<th>Geometric Least Squares Means</th>
<th>90% Confidence Interval</th>
<th>Power (%)</th>
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</thead>
<tbody>
<tr>
<td>Test Product-T</td>
<td>621.596</td>
<td>92.02 - 108.00</td>
<td>99.8</td>
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<tr>
<td>Reference Product-R</td>
<td>623.523</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ratio (T/R)%</td>
<td>99.7</td>
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<td>-</td>
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<tr>
<td>lnC&lt;sub&gt;max&lt;/sub&gt;</td>
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<tr>
<td>lnAUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>1295.041</td>
<td>89.15 - 101.43</td>
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<tr>
<td>lnAUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>1231.474</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Evaluation
The 90% confidence intervals were within the bioequivalence acceptance limits of 80.00 – 125.00 %.

The bioequivalence study was designed, conducted and analysed in accordance with CPMP/EWP/QWP/1401/98/Rev 1.
All outstanding quality points for clarification were resolved and bioequivalence between Clopidogrel 75 mg Film-coated Tablets and the reference innovator, Plavix 75 mg Film-Coated tablets, was demonstrated. This variation application was approvable from a clinical and quality point of view.

Decision - Granted
Date 03/11/2014