# Clopidogrel 75 mg film-coated tablets

**PL 40378/0180**

## UKPAR

## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>5</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>15</td>
</tr>
<tr>
<td>Steps taken after authorisation</td>
<td>16</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>17</td>
</tr>
<tr>
<td>Patient Information Leaflet</td>
<td>18</td>
</tr>
<tr>
<td>Labelling</td>
<td>19</td>
</tr>
</tbody>
</table>
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Clopidogrel 75 mg film-coated tablets. It explains how Clopidogrel 75 mg film-coated tablets (PL 40378/0180, previously PL 33410/0118) were assessed and the authorisation recommended, as well as the 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 package leaflet 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 75mg film-coated Tablets (Sanofi Pharma/Bristol-Myers Squibb SNC).

Clopidogrel 75 mg film-coated tablets contain the active ingredient, clopidogrel (as clopidogrel bisulphate). Clopidogrel 75 mg 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).

Clopidogrel 75 mg film-coated tablets are prescribed to help prevent blood clots and reduce the risk of these severe events in patients who have a condition of hardening of arteries (also known as artherosclerosis), 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 the doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. The patient should also be given acetylsalicylic acid (acetylsalicylic acid), a substance present in many medicines used to relieve pain and lower fever as well as to prevent blood clotting, by the doctor, or
• have an irregular heartbeat, a condition called ‘atrial fibrillation’, and who cannot take medicines known as ‘oral anticoagulants’ (vitamin K antagonists) which prevent new clots from forming and prevent existing clots from growing. The patient should have been told that ‘oral anticoagulants’ are more effective than aspirin or the combined use of Clopidogrel 75 mg film-coated tablets l and aspirin for this condition. The doctor should prescribe Clopidogrel 75 mg film-coated tablets plus acetylsalicylic acid if the patient cannot take ‘oral anticoagulants’ and does not have a risk of major bleeding.

How do Clopidogrel 75 mg film-coated tablets work?
The active ingredient, clopidogrel, belongs 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 can only be obtained on prescription. This medicine should be taken exactly as advised by the prescribing doctor.

Clopidogrel 75 mg film-coated tablets are taken by mouth with or without food.
The recommended dose in the treatment of severe chest pain (unstable angina or heart attack) is 300 mg of clopidogrel (4 tablets of 75 mg) once at the start of treatment, followed by a usual dose of 75 mg of clopidogrel per day to be taken at the same time each day.

Clopidogrel 75 mg film-coated tablets should be taken for as long as prescribed by the doctor.

For further information on how Clopidogrel 75 mg film-coated tablets are used, please see the Summary of Product Characteristics available on the MHRA website.

What benefits of Clopidogrel 75 mg film-coated tablets have been shown in studies? As Clopidogrel 75 mg film-coated tablets are a generic medicine, studies in patients have been limited to tests to determine that the tablets are similar to the reference medicine, Plavix 75mg film-coated Tablets (Sanofi Pharma/Bristol-Myers Squibb SNC). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the original Marketing Authorisation Holder (APSLA Limited) provided data from the published literature on clopidogrel.

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, the benefits and possible side effects are taken as being the same as those for the reference medicine.

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 75mg film-coated Tablets (Sanofi Pharma/Bristol-Myers Squibb SNC). Therefore, the MHRA decided that, as for Plavix 75mg film-coated Tablets (Sanofi Pharma/Bristol-Myers Squibb SNC), the benefits are greater than the risks and recommended that it can be approved for use.

For the full list of restrictions, see the package leaflet.

What measures are being taken to ensure the safe and effective use of Clopidogrel 75 mg film-coated tablets? Safety information has been included in the Summary of Product Characteristics and the package leaflet for Clopidogrel 75 mg film-coated tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Clopidogrel 75 mg film-coated tablets. A Marketing Authorisation (PL 33410/0118) was first granted in the UK to ASPLA Limited on 16 June 2011.

Subsequent to a Change of Ownership procedure, the Marketing Authorisation (PL 40378/0180) was granted to Aptil Pharma Limited on 21 November 2012.

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 package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2014.
Clopidogrel 75 mg film-coated tablets

PL 40378/0180

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction ........................................... Page 6
Pharmaceutical assessment ......................... Page 8
Non-clinical assessment .............................. Page 11
Clinical assessment .................................. Page 12
Overall conclusion and benefit-risk assessment  Page 15
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted APSLA Limited a Marketing Authorisation for the medicinal product, Clopidogrel 75 mg film-coated tablets (PL 33410/0118) on 16 June 2011. The product is a prescription-only medicine (POM).

This is a generic application for Clopidogrel 75 mg film-coated tablets, submitted under Article 10.1 of Directive 2001/83/EC, as amended. The reference product is Plavix 75mg film-coated Tablets (EM 15713/0004; Sanofi Pharma/Bristol-Myers Squibb SNC), which was registered via the Centralised Procedure on 15th July 1998. The reference product has been authorised in the European Community for more than 10 years, thus the period of data exclusivity has expired.

Clopidogrel 75 mg film-coated tablets contain the active ingredient, clopidogrel (as clopidogrel bisulphate), belonging to the class of drugs known as platelet aggregation inhibitors (excluding heparin) – ATC code B01AC04. Clopidogrel is indicated for the 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.

Clopidogrel is also indicated for the prevention of atherothrombotic and thromboembolic events 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.

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 P2Y\textsubscript{12} 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.

Following single and repeated oral doses of 75mg per day, clopidogrel is rapidly absorbed with peak plasma levels expected approximately one hour after dosing. Mean peak plasma concentrations of the parent compound are very low (approximately 2.2-2.5 ng/ml) approximately 45 minutes after dosing. Urinary excretion of clopidogrel metabolites suggests absorption is at least 50%. Clopidogrel is an inactive prodrug and is extensively metabolised by the liver. The main metabolite is an inactive carboxylic acid derivative (SR26334) representing 85% of the circulating compound in plasma. The active metabolite is a thiol derivative, which has not been detected in plasma. This metabolite, isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.
The kinetics of the main circulating metabolite are linear in the dose range of 50 to 150 mg of clopidogrel. *In vitro* studies demonstrated that clopidogrel and the major metabolite are highly protein bound (98% and 94% respectively). The binding is non-saturable *in vitro* over a wide concentration range.

Clopidogrel is excreted in the urine and faeces. After an oral dose of $^{14}$C-labelled clopidogrel in man, approximately 50% was excreted in the urine and 46% in the faeces. Elimination half-life of the major metabolite was 8 hours.

No new non-clinical or clinical efficacy studies were conducted, which is acceptable given that these are generic applications cross-referring to a product that has been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Clopidogrel 75 mg film-coated tablets (clopidogrel bisulphate), to that of the reference product, Plavix 75mg film-coated Tablets (clopidogrel hydrogen sulphate). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. Routine pharmacovigilance activities according to Volume 9A of the rules governing medicinal products in the EU will be undertaken whilst the product is on the market; this is considered satisfactory. The reference product has been in use for many years and the safety profile of the active is well-established. The excipients used in the medicinal product are well-established and meet EU quality requirements.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). Clopidogrel is a well-established active substance that has had widespread clinical use for many years. These were applications for a generic product, which will not be administered at a higher dosage, for a longer duration or for different indications than were previously authorised. There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.

Subsequent to a Change of Ownership procedure, the Marketing Authorisation (PL 40378/0180) was granted to Aplet Pharma Limited on 21 November 2012.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Clopidogrel

Nomenclature:

INN: Clopidogrel

Chemical name:

i) Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S), sulphate (1:1)

ii) Methyl (+)-(S)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate, sulphate (1:1)

Structure:

![Structure of Clopidogrel]

Physical form: A white to off-white powder

Solubility: Freely soluble in methanol, practically insoluble in ether

The active substance, clopidogrel, is not the subject of a European Pharmacopoeia (Ph. Eur.) monograph. A monograph however exists for clopidogrel bisulfate in the United States Pharmacopoeia.

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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been 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 specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer.

Clopidogrel active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the 36-month retest period that has been applied.
MEDICINAL PRODUCT

Description & Composition

Clopidogrel 75 mg film-coated tablets are presented as pink-coloured, circular, biconvex, film-coated tablets, plain on both sides. Each tablet contains 97.854 mg of clopidogrel bisulphate equivalent to 75 mg of clopidogrel.

Other ingredients consist of pharmaceutical excipients, namely mannitol E421, crospovidone, colloidal anhydrous silica, microcrystalline cellulose, macrogol 6000 and hydrogenated castor oil making up the tablet core; and hypromellose (E464), titanium dioxide (E171), macrogol/PEG400, iron oxide red (E172) and polysorbate 80 (E433) comprising the ‘Opadry YS-1-14778-A Pink’ film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet core comply with their respective European Pharmacopoeia monographs. The Opadry formulation used for film-coating is controlled to in-house specifications. It is constituted from pharmacopeial ingredients plus the colourant iron oxide, red (E172), which complies with EU colouring regulation 95/45/EC. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a stable, generic medicinal product, bioequivalent to the reference product, Plavix 75mg film-coated Tablets (EM 15713/0004; Sanofi Pharma/Bristol-Myers Squibb SNC).

Comparative dissolution and impurity data were provided for batches of the test product and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the manufacturing process. Process validation studies were conducted on pilot-scale batches and the results were satisfactory. The MAH has provided a commitment to provide data for validation performed on full-scale batches.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in 3-ply aluminium-aluminium laminated film and plain aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in a pack size of 30 film-coated tablets.
Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. 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. These data support a shelf-life of 2 years, with the storage instructions ‘Store in the original package’.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The user-testing of the PIL has been evaluated and is accepted. The labelling fulfils the statutory requirements for Braille.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Clopidogrel 75 mg film-coated tablets from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

This abridged application, submitted under Article 10.1 of Directive 2001/83/EC, as amended, is for Clopidogrel 75 mg film-coated tablets, claiming to be a generic product of Plavix 75mg film-coated Tablets (EM 15713/0004; Sanofi Pharma/Bristol-Myers Squibb SNC).

No new non-clinical data have been supplied with this application and none are required for this type of application. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

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

**CLINICAL BACKGROUND**
Clopidogrel hydrochloride (d-methyl[2-chlorophenyl]-5-[4,5,6,7-tetrahydrothieno][3,2-c pyridinyl] acetate hydrochloride) is a thienopyridine prodrug used clinically to inhibit ADP-induced platelet aggregation. It reduces the risk of thrombotic events in patients with a history of atherosclerotic diseases, such as stroke or myocardial infarction.

**INDICATIONS**
Clopidogrel is indicated for the **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.

Clopidogrel is also indicated for the **prevention of atherothrombotic and thromboembolic events** 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.

The indications are consistent with those for the reference product and are satisfactory.

**POSOLOGY AND METHOD OF ADMINISTRATION**
Full details concerning the posology are provided in the SmPC. The posology is satisfactory.

**TOXICOLOGY**
The toxicology of clopidogrel is well-known. No new data have been submitted and none are required for this type of application.

**CLINICAL PHARMACOLOGY**
The clinical pharmacology of clopidogrel is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.

**Pharmacokinetics – bioequivalence study**
The applicant has conducted a single bioequivalence study comparing the pharmacokinetic profiles of Clopidogrel 75 mg film-coated tablets (test) and Plavix 75mg film-coated Tablets, Sanofi Pharma (reference, clopidogrel hydrochloride).

Based on EMEA guidance, data from the parent compound are usually considered more sensitive to detect differences between formulations than those of the metabolite(s). The reason for this is that $C_{\text{max}}$ of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than $C_{\text{max}}$ of a metabolite. It may also be explained that data from the parent compound are a
reflection of the absorption process, ruled in part by the performance of the formulation. Since the objective of a bioequivalence study is to compare the performance of the test and reference formulations, evaluation of bioequivalence should generally be based upon measured concentrations of the parent compound.

Clopidogrel is extensively metabolised by the liver to the carboxylic acid derivative, which is inactive. This metabolite is thus formed after absorption of the parent clopidogrel, and consequently the plasma concentrations of the carboxylic acid metabolite are directly related to the plasma concentrations of clopidogrel. This assumption is supported by the kinetics of the carboxylic acid metabolite that are linear (plasma concentrations increased in proportion to dose of clopidogrel). Hence, it is deemed appropriate to demonstrate bioequivalence based on parent clopidogrel data only since this analyte only represents a direct reflection of the performance of the formulation.

The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products.

This was an open-label, randomised, single-dose, 2-way crossover bioavailability and bioequivalence study conducted in 24 healthy human male subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 48.0 hours after administration of test or reference product. Plasma levels of the prodrug, clopidogrel, were detected by a validated LC-MS/MS bioanalytical method.

The primary pharmacokinetic parameters for this study were \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \). Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed \( C_{\text{max}} \), \( \text{AUC}_{0-\infty} \), and \( \text{AUC}_{0-\infty} \).

Results:
24 subjects were enrolled in the study; 22 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation and non-inclusion in the pharmacokinetic analysis of two subjects was satisfactorily justified.

Safety – There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (X)</td>
<td>Test Product (Y)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>2.08</td>
<td>2.03</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) (ng.h/ml)</td>
<td>4.73</td>
<td>4.77</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng.h/ml)</td>
<td>5.88</td>
<td>5.68</td>
</tr>
</tbody>
</table>
Assessor's comment:
Considering the PK data for clopidogrel, bioequivalence has been adequately demonstrated, with 90% confidence intervals between 80 and 125% for Cmax and AUC0-t. Since AUC0-t covers less than 80% of AUC0-inf in less than 20% of observations, it is acceptable to rely on AUC0-t rather than AUC0-inf.

Conclusion on Bioequivalence
The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for Cmax and AUC0-t for clopidogrel fall within the acceptance criteria ranges of 80.00-125.00% in line with current CHMP guidelines.

CLINICAL EFFICACY
No new data have been submitted and none are required. The reference product is established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of clopidogrel is well-established from its extensive use in clinical practice.

CLINICAL SAFETY
No new safety data have been submitted and none are required for this type of application. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of clopidogrel is well-known.

CLINICAL OVERVIEW
A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPC is satisfactory.

Patient Information Leaflet (PIL)
The final PIL is in line with the approved SmPC and is satisfactory. The PIL user-testing has been evaluated and is accepted.

Labelling
The labelling is satisfactory.

CONCLUSION
Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
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 this type of application.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Clopidogrel 75 mg film-coated tablets and the reference product, Plavix 75mg film-coated Tablets (Sanofi Pharma).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is satisfactory.

The final PIL is in line with the SmPC and is satisfactory. 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 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.

Mock-ups of the labelling have been provided. The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Clopidogrel 75 mg film-coated tablets is a generic version of the reference product, Plavix 75mg film-coated Tablets (EM 15713/0004; Sanofi Pharma/Bristol-Myers Squibb SNC). Extensive clinical experience with clopidogrel is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Clopidogrel 75 mg film-coated tablets

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 5 May 2010.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 27 May 2010.

3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 20 July 2010 and further information relating to the quality dossier on 23 August 2010.

4 The applicant responded to the MHRA’s requests, providing further information for the clinical sections on 13 September 2010 and further information for the quality sections on 14 December 2010.

5 The application was granted on 16 June 2011.
SUMMARY OF PRODUCT CHARACTERISTICS
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

The Marketing Authorisation Holder, Aptil Pharma Limited, has submitted the text version only and has committed to submitting mock-up livery to the regulatory authorities for approval before packs are marketed.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| CARTON |

1. **NAME OF THE MEDICINAL PRODUCT**

Clopidogrel 75 mg Film-coated tablets
Clopidogrel

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each Film-coated tablet contains 97.854 mg of clopidogrel bisulphate equivalent to 75 mg of clopidogrel

3. **LIST OF EXCIPIENTS**

Also contains hydrogenated castor oil. See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets
30 tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

Exp: MM/YYYY

9. **SPECIAL STORAGE CONDITIONS**

Store in original package.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

**PL Holder:**
Aptil Pharma Limited, 9th Floor, CP House, 97-107 Uxbridge Road, Ealing, London W5 5TL

**Distributed By:**
APC Pharmaceuticals & Chemicals (Europe) Limited, 9th Floor, CP House, 97-107 Uxbridge Road, Ealing, London W5 5TL

12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 40378/0180

13. **BATCH NUMBER**

   Lot: xxxxxx

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   [POM]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

   Clopidogrel 75 mg Film-coated tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTERS</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 75 mg Film-coated tablets</td>
</tr>
<tr>
<td>Clopidogrel bisulphate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aptil Pharma Limited</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp: MM/YYYY</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot: xxxxxx</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>