Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Clopidogrel 75mg film-coated tablets

clopidogrel hydrogen sulfate

PL 51463/0193

KENT PHARMA UK 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. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

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?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Plavix 75 mg film-coated tablets.

Clopidogrel is 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).

Patients are prescribed Clopidogrel to help prevent blood clots and reduce the risk of these severe events in the follow circumstances:

- hardening of arteries (also known as atherosclerosis)
- previously experienced a heart attack, stroke or have a condition known as peripheral arterial disease
- a severe type of chest pain known as ‘unstable angina’ or ‘myocardial infarction’ (heart attack). For the treatment of this condition, the patient’s doctor may have placed a stent in the blocked or narrowed artery to restore effective blood flow. The patient may 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 their doctor.
- symptoms of a stroke which go away within a short period of time (also known as transient ischemic attack) or an ischemic stroke mild in severity. Patients may also be given acetylsalicylic acid by their doctor starting within the first 24 hours.
- 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 and acetylsalicylic acid for this condition. The patient’s doctor should have prescribed clopidogrel plus acetylsalicylic acid if the patient cannot take ‘oral anticoagulants’ and they do not have a risk of major bleeding.

How do Clopidogrel 75 mg film-coated tablets work?
Clopidogrel Tablets contains Clopidogrel and 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 75 mg film-coated tablets used?
The pharmaceutical form of this medicine is film-coated tablets and the route of administration is oral (by mouth). Clopidogrel may be taken with or without food

The recommended dose, including for patients with a condition called 'atrial fibrillation' (an irregular heartbeat), is one 75 mg tablet of clopidogrel per day to be taken orally with or without food, and at the same time each day.

If a patient has experienced severe chest pain (unstable angina or heart attack), their doctor may give them 300 mg or 600 mg of clopidogrel (1 or 2 tablets of 300 mg or 4 or 8 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of clopidogrel per day as described above.

If a patient has experienced symptoms of a stroke which go away within a short period of time (also known as transient ischemic attack) or an ischemic stroke mild in severity, the doctor may recommend 300 mg of clopidogrel (1 tablet of 300 mg or 4 tablets of 75 mg) once at the start of treatment. Then, the recommended dose is one 75 mg tablet of clopidogrel per day as described above with acetylsalicylic acid for 3 weeks. Then the physician would prescribe either clopidogrel alone or acetylsalicylic acid alone. The patient should take clopidogrel for as long as their doctor continues to prescribe it.

For further information on how Clopidogrel 75 film-coated tablets are used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Clopidogrel 75 mg film-coated tablets have been shown in studies?
Because Clopidogrel 75 mg film-coated tablets is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. 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?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Clopidogrel 75 mg film-coated tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why were Clopidogrel 75 mg film-coated tablets approved?
It was concluded that, Clopidogrel 75 mg film-coated tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Clopidogrel 75 mg film-coated tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Clopidogrel 75 mg film-coated tablets. The RMP details the important risks of Clopidogrel 75 mg film-coated tablets, how these risks can be minimised, any uncertainties about Clopidogrel 75 mg film-coated tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Clopidogrel 75 mg film-coated tablets:

Summary of safety concerns	
Important identified risks	Major bleeding (including ICH[a])
Important potential risks	None
Missing information	None

[a]ICH is applicable especially in TIA/MS indication of DAPT for the first 21 days after TIA/MS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Clopidogrel 75 mg film-coated tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Clopidogrel 75 mg film-coated tablets
A marketing authorisation for Clopidogrel 75 mg film-coated tablets was granted in the United Kingdom (UK) on 2 July 2024.

The full PAR for Clopidogrel 75 mg film-coated tablets follows this summary.

This summary was last updated in August 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Clopidogrel 75 mg film-coated tablets (PL 51463/0193) could be approved.

The product is approved for the following indications.

Secondary prevention of atherothrombotic events
Clopidogrel is indicated in:

- Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic 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 patients undergoing percutaneous coronary intervention (including patients undergoing a stent placement) or medically treated patients eligible for thrombolytic/fibrinolytic therapy.

In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)
Clopidogrel in combination with ASA is indicated in adult patients with moderate to high-risk TIA (ABCD2[1] score ≥ 4) or minor IS (NIHSS[2] ≤ 3) within 24 hours of either the TIA or IS event.

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.

[1] Age, Blood pressure, Clinical features, Duration, and Diabetes mellitus diagnosis
[2] National Institutes of Health Stroke Scale

For more information on the indications of this medicine, please see the Summary of Product Characteristics available on the MHRA website.

The active ingredient in this medicine is clopidogrel hydrogen sulfate.

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet

aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Plavix 75 mg film-coated tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

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

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

A marketing authorisation for Clopidogrel 75 mg film-coated tablets was granted in the United Kingdom (UK) on 2 July 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 75 mg of clopidogrel (as hydrogen sulphate).

In addition to clopidogrel hydrogen sulfate, this product also contain the excipients:

- Tablet core: silica colloidal anhydrous, macrogol 6000, mannitol (E421), cellulose, microcrystalline 14, low substituted hydroxypropyl cellulose (LH-11), crospovidone, hydrogenated castor oil, sodium stearyl fumarate.
- Tablet coating: Opadry II 32K540130 Pink, Purified Water.
- Tablet polishing: carnauba wax.

The finished product is packaged in in Alu Alu blister composed of Alu Alu cold form laminate and Aluminium Foil in cardboard cartons containing 28 and 30 film-coated tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

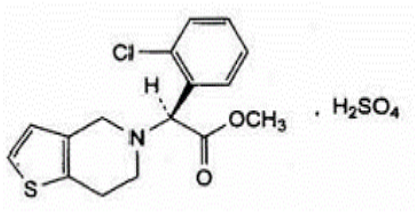
II.2 ACTIVE SUBSTANCE

rINN: clopidogrel hydrogen sulfate

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

Molecular Formula: C16H18ClNO6S2

Chemical Structure:



Molecular Weight: 419.9

Appearance: White or almost white powder

Solubility: Freely soluble in methanol and practically insoluble in cyclohexane, freely soluble in water at pH 1, Practically insoluble in water at neutral pH.

Clopidogrel hydrogen sulfate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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

Satisfactory batch formulation data 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 Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months, with no special storage conditions is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of clopidogrel hydrogen sulfate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of clopidogrel hydrogen sulfate is well-known. With the exception of data from bioequivalence study C1B01983, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

<u>Bioequivalence Study C1B01983 (single oral dose; fasted)</u>

This study was an open label, randomised, four-period, two-treatment, two-sequence, fully replicate, crossover, balanced, single dose oral bioequivalence study comparing the test product Clopidogrel 75 mg Tablets versus the reference product Plavix 75 mg Tablets subjects/patients under fasted/fed conditions.

After at least an overnight fasting of at least 8 hours, a single 75 mg oral dose of investigational product was administered to the subjects as per the randomisation schedule. A standard meal was served at least 4 hours after dosing. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of at least 5 days between the treatment periods.

A summary of the pharmacokinetic results is presented on the following page.

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%*
AUCt	106.18%	(95.57%;117.96%)	39.840%
Cmax	103.70%	(92.77%;115.91%)	42.345%

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
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 benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**