CBG MEB

Public Assessment Report

Scientific discussion

Clopidogrel CF 75 mg, film-coated tablets

(clopidogrel hydrogen sulphate)

NL/H/3520/001/DC

Date: 24 July 2017

This module reflects the scientific discussion for the approval of Clopidogrel CF 75 mg, film-coated tablets. The procedure was finalised on 2 August 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Clopidogrel CF 75 mg, film-coated tablets from Centrafarm B.V.

The product is indicated for:

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.
- In 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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Plavix 75 mg film-coated tablets which has been registered by Sanofi Pharma Bristol-Myers Squibb SNC since 16 July 1998 through centralised procedure (EU/1/98/069/002A).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Ireland, Luxembourg, Portugal and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Clopidogrel CF is a pink coloured, round, biconvex, bevelled edged film-coated tablet.

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate).

The film-coated tablets are packed in PVC/Aclar-aluminium blisters and HDPE containers closed with polypropylene stock ribbed closures with wad having induction–sealing liner and containing silica gel sachets.

The excipients are:
Tablet core - mannitol (E 421), microcrystalline cellulose (E 460), hydroxylpropyl cellulose (E 463), macrogol 6000 (E 1521), crospovidone (E 1202) and hydrogenated castor oil
Film-coating - lactose monohydrate, hypromellose (E 464), titanium dioxide (E 171), triacetin (E 1518) and red iron oxide (E 172)

II.2 Drug Substance

The active substance is clopidogrel hydrogen sulphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water. The active

substance exists in different polymorphic forms. The active substance manufacturer produces polymorphic form I. Clopidogrel contains an asymmetric carbon leading to two enantiomers. The active substance is manufactured as the (2S) enantiomer. The (2R) enantiomer is controlled as an impurity.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional requirements for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for four commercial scale batches.

Stability of drug substance
The active substance is stable for 18 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Development focused on the granulation step for which finally a roll compaction process was chosen. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

The MAH submitted one bioequivalence study. Composition and manufacture of the batch used in the bioequivalence study are identical to those proposed for commercial production. Dissolution profiles of the biobatches in 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer support bioequivalence.

Manufacturing process
The manufacturing process involves the production of intra-granules which are prepared by mixing, lubrication, compaction and sizing. The prepared dry granules are mixed with the remaining extra granular ingredients and the final blend is compressed to yield the core tablets which are subsequently film coated. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of the minimum proposed commercial batch size and three batches of a medium commercial batch size of the first site and with three batches of a medium commercial batch size at the second site, in accordance with the relevant European guidelines. A risk based process validation protocol for full scale batches has been provided.

Control of excipients
With the exception of the coating material, excipients are tested according to the Ph.Eur. or United States Pharmacopoeia National Formulary (USP-NF). An acceptable specification is provided for the coating material. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, water, dissolution, uniformity of dosage units, related substances, assay, and microbial contamination. The release and

shelf life limits differ for related substances, assay, and dissolution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the first manufacturing site on six commercial scale batches and from the second manufacturing site on the three commercial scale batches have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on three batches of the smallest proposed commercial batch size manufactured by the first manufacturing site and stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months), and 40°C/75% RH (6 months) and on three batches of a medium commercial batch size of the second site stored at 25°C/60% RH (3 months) and 40°C/75% RH (3 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packagings.
At accelerated conditions, a significant increase in the content of related substances was observed after six months. Compliance with the limits of the tested parameters after 12 months at intermediate and 24 months at long term conditions was confirmed. The drug product was shown to be photostable. Based on the provided results, a shelf-life of 24 months can be approved for the drug product packed in PVC/Aclar–Alu blisters and HDPE containers when stored below 30°C.
An in-use stability study in the HDPE containers of 1000's count was performed at the beginning and towards the end of the shelf life with two batches of the first manufacturing site and at the beginning of the shelf life with two batches of the second manufacturing site packed in HDPE containers of 30's and 1000's count. Based on trends in impurity levels, an in-use shelf life of six months is proposed which is considered justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The coating material contains lactose monohydrate. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Clopidogrel CF 75 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Clopidogrel CF 75 mg, film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Plavix which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clopidogrel hydrogen sulphate is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Clopidogrel CF 75 mg, film-coated tablets (Centrafarm BV, the Netherlands) is compared with the pharmacokinetic profile of the reference product Plavix 75 mg film-coated tablets (Sanofi Clir SNC, France).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A two-way, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-43 years. Each subject received a single dose (75 mg) of one of the 2 clopidogrel formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10, 12, 16, 20, 24, 30 and 36 hours after administration of the products.

The design of the study is acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. As this product can be taken regardless food intake, a study under fasting conditions is justified. The pharmacokinetic parameters are supported by data on the metabolite clopidogrel acid.

Clopidogrel may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of clopidogrel. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 60 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clopidogrel under fasted conditions.

Treatment N=60	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	3136 ± 5667	3375 ± 5867	1600 ± 2986	0.83 (0.4 - 1.5)	3.62 ± 3.46
Reference	2579 ± 3784	2808 ± 3956	1430 ± 2462	1.0 (0.5 - 2.0)	4.57 ± 5.35
***Ratio (90% CI)**	1.05 (0.95 - 1.15)	1.03 (0.94 - 1.13)	1.01 (0.91 - 1.13)	--	--
CV (%)	31	32	37	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clopidogrel acid under fasted conditions.

Treatment N=60	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	9361 ± 2610	10263 ± 2774	3517 ± 914	0.67 (0.5 - 2.5)	8.7 ± 3.0
Reference	9129 ± 2619	10126 ± 2860	3457 ± 975	0.68 (0.5 -1.5)	9.4 ± 5.1
***Ratio (90% CI)**	1.03 (1.00 - 1.05)	1.02 (0.99 - 1.04)	1.02 (0.96 - 1.09)	--	--
CV (%)	8.4	9.0	21	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Clopidogrel CF 75 mg film-coated tablets is considered bioequivalent with Plavix 75 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clopidogrel CF.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Bleeding and haematological disorders • Reduced efficacy of clopidogrel in poor CYP2C19 metabolisers • Reduced efficacy of clopidogrel due to interactions • Hypersensitivity reactions, incl. cross-reactive drug hypersensitivity among thienopyridines • Eosinophilic pneumonia
Important potential risks	None
Missing information	• Use in pregnant and lactating women • Use in the paediatric population • Use in patients with moderate/severe hepatic impairment • Use in severe renal impaired patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Plavix. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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. The test consisted of: a pilot test with 3 participants, followed by a rounds with 20 participants. The 21 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Clopidogrel CF 75 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Plavix 75 mg film-coated tablets. Plavix is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Clopidogrel CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 August 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3520/ 001/IB/001	Product name change in Germany	Product name	8-12-2016	Approval	Amend the invented product name of the medicinal product in Germany from "Clopidogrel ALIUD 75 mg Filmtabletten" to "Clopidogrel AL 75 mg Filmtabletten".
NL/H/3520/ 001/IB/002/ G	Product name change in Sweden	Product name	8-3-2017	Approval	Amend the invented name of the finished product in Sweden from "Clopidogrel STADA Arzneimittel AG 75 mg filmdragerade tabletter" to "Clopidogrel STADA 75 mg filmdragerade tabletter".
NL/H/3520/ 001/IA/003	Additional packaging site	--	24-3-2017	Approval	An additional packaging site is proposed for secondary packaging.
NL/H/3520/ 001/IB/004	Product name change in Luxembourg	Product name	16-6-2017	Approval	Amend the invented name of the finished product in Luxembourg from "Clopidogrel Eurogenerics" to "Clopidogrel EG"
NL/H/3520/ 001/IA/005	Change in packaging	--	16-6-2017	Approval	Change in immediate packaging of the finished product, qualitative and quantitative composition: addition of oPA/Aluminium/PVC-Aluminium

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)