

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Clopidogrel Aurobindo 75 mg, film-coated tablets
Aurobindo Pharma B.V., the Netherlands**

clopidogrel (as hydrogen sulphate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2763/001/MR
Registration number in the Netherlands: RVG 106384**

16 May 2013

Pharmacotherapeutic group:	platelet aggregation inhibitors excl. heparin
ATC code:	B01AC04
Route of administration:	oral
Therapeutic indication:	prevention of atherothrombotic events; myocardial infarction; ischaemic stroke; established peripheral arterial disease; acute coronary syndrome; prevention of atherothrombotic and thromboembolic events in atrial fibrillation
Prescription status:	prescription only
Date of first authorisation in NL:	26 October 2010
Concerned Member States:	Mutual recognition procedure with DE, DK, ES, FR, IT, MT, NO, PT, RO, SE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Clopidogrel Aurobindo 75 mg, film-coated tablets from Aurobindo Pharma B.V. The date of authorisation was on 26 October 2010 in the Netherlands.

The product is indicated for:

Prevention of atherothrombotic events

Clopidogrel Aurobindo is indicated 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.

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, who 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 SPC.

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes including CYP2C19 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.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Plavix 75 mg film-coated tablets, which has been registered in the EEA since 15 July 1998 through a centralised procedure (EMEA/H/C/000174) by Sanofi Pharma Bristol-Myers Squibb SNC (original product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Plavix 75 mg film-coated tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different

excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is clopidogrel hydrogen sulphate, an established active substance described in the European Pharmacopoeia (Ph.Eur*). It is a white or almost white powder, which is freely soluble in methanol and in water, and practically insoluble in cyclohexane. The active substance exists in different polymorphic forms. Polymorph form I is used. Clopidogrel contains an asymmetric carbon leading to two enantiomers. The active substance is manufactured as the (S)-(+)-enantiomer.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The active substance is manufactured in a two stage synthesis. No class 1 organic solvents are used and no heavy metal catalysts are involved. The active substance has been adequately characterized.

Quality control of drug substance

The drug substance specification of the MAH is in line with the Ph.Eur. and ICH requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analysis data demonstrating compliance with the drug substance specification were presented for three commercial-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three commercial-scale batches stored at 30°C/65% RH (twelve months) and at 40°C/75% RH (six months). All parameters met the specification. No trend has been observed for any of the parameters. The proposed re-test period of 12 months without precautions for storage temperature is justified.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Clopidogrel Aurobindo 75 mg is a pink coloured, round, biconvex, bevel edge, film-coated tablet debossed with 'E' on one side and '34' on the other side. Each film-coated tablet contains 75 mg of clopidogrel (as clopidogrel bisulfate).

The film-coated tablets are packed in PVC/Aclar-aluminium blister packs or HDPE containers.

The excipients are: cellulose microcrystalline, mannitol, low-substituted hydroxypropyl cellulose, crospovidone (type A), macrogol 6000, hydrogenated castor oil, and the coating material Opadry (pink). which consists of lactose monohydrate, hypromellose, titanium dioxide, triacetin and iron oxide red.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Development focussed on the granulation step for which finally a roll compaction process was chosen. The choices of the packaging and manufacturing process are justified. Composition and manufacture of the batch used in the bioequivalence study are identical to those proposed for commercial production. Dissolution of the generic and reference product was comparable at three pH values. The pharmaceutical development of the product has been adequately performed.

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 extragranular ingredients and the final blend is compressed to the desired size to yield the core tablets. These are film coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two batches of the minimum proposed commercial batch size.

Control of excipients

With the exception of the coating material, the excipients comply with the Ph.Eur or the USP/NF. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, average weight, water, dissolution, uniformity of dosage units, related substances, assay, thickness, identification of colourants, and microbial contamination. The release and shelf life limits differ for related substances and the fact that no shelf life limit for thickness has been included. The drug product specifications are acceptable.

Batch analytical data from the proposed production site have been provided on two batches of the minimum proposed commercial batch size demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on two batches of the minimum proposed commercial batch size stored at 25°C/60% RH (18 months), 30°/65% RH (12 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/Aclar-aluminium blisters and HDPE containers. In addition, stability of bulk product was investigated at 25°C/60% RH (12 months).

At accelerated conditions, a significant increase in the content of related substances as observed. Compliance with the limits of the tested parameters after 12 months at intermediate and 18 months at long term conditions was confirmed. Photostability was demonstrated.

An in-use stability study in the HDPE containers of 1000's count was performed during which a significant increase in the levels of related substances was observed after 18 months at long term conditions.

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. In-use shelf life for the HDPE containers is 6 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Except for lactose which is used in preparation of the coating material, all excipients are free from any raw material of animal or human origin and comply with the requirements of the relevant Directive and

guidelines with regard to TSE issues. As for the lactose component, a vendor's suitable certificate was provided to confirm that it is produced from milk obtained from healthy animals in the same conditions as used for milk for human consumption.

II.2 Non-clinical aspects

This product is a generic formulation of Plavix, which is available on the European market. 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.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of clopidogrel released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Clopidogrel 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, several bioequivalence studies were submitted by MAH during the national registration procedure in the Netherlands. However, after registration of the product the MAH conducted a new bioequivalence, as there was a change in the excipients. This study was approved through a Type II variation and is the only study discussed below, since it was the basis for this Mutual Recognition Procedure.

In the bioequivalence study the pharmacokinetic profile of the test product Clopidogrel Aurobindo 75 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Plavix 75 mg film-coated tablets (Sanofi Pharma BMS, France).

The choice of the reference product

The reference product is acceptable, as Plavix is registered through a centralised procedure. It is therefore considered identical across the EEA member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, 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 of water, after an overnight fasting period. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected for the determination of clopidogrel and clopidogrel acid pre-dose and at 0.16, 0.33, 0.5, 0.67, 0.83, 1.0, 4.1, 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 and conduct of the study are acceptable. The population studied is considered appropriate.

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

There were no drop-outs. Plasma samples of all 60 subjects which enrolled in the study were analysed.

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

Treatment N=60	AUC _{0-t} pg.h/ml	AUC _{0-∞} pg.h/ml	C _{max} pg/ml	t _{max} h	t _{1/2} h
Test	3136 \pm 5666	3375 \pm 5866	1600 \pm 2985	0.83 (0.5 - 1.5)	3.62 \pm 3.46
Reference	2579 \pm 3783	2808 \pm 3955	1430 \pm 2462	1.0 (0.5 - 2.0)	4.57 \pm 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-∞} 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					

**In-transformed values*

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

Treatment N=60	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	9361 \pm 2609	10263 \pm 2773	3517 \pm 914	0.67 (0.5 - 2.5)	8.7 \pm 3.0
Reference	9129 \pm 2619	10126 \pm 2859	3457 \pm 974	0.68 (0.5 - 1.5)	9.4 \pm 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-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of clopidogrel under fasted conditions, supported by data on the metabolite clopidogrel acid, it can be concluded that Clopidogrel Aurobindo 75 mg and Plavix 75 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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.

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).

Risk management plan

Clopidogrel was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of clopidogrel can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. The MAH committed to file a variation to add the RMP within 2 months after finalisation of the MRP.

Product information

SPC

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Plavix. A paediatric program was conducted to evaluate the efficacy of clopidogrel for the reduction of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. The results of these studies and relevant recommendations are included in the SPC as it is included in the SPC for Plavix.

Readability test

No user testing of the PIL of Clopidogrel Aurobindo has been performed. A bridging statement has been submitted with reference to the PIL of another clopidogrel generic, for which a readability test was approved. This PIL has a similar layout and design. Product specific information in this latter PIL deviates from the information in the PIL of the current product. However, the content of the PIL of Clopidogrel Aurobindo is similar to the PIL of Plavix, which has also been successfully user-tested. Therefore, the absence of a readability test is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Clopidogrel Aurobindo 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 11 January 2013.

The date for the first renewal will be: 26 October 2015.

There were no post-approval commitments made during the procedure:

Quality - medicinal product

- The MAH committed to perform validation of the manufacturing process on the largest batch size.
- The MAH committed to continue the ongoing long term stability studies of the submission batches, to carry out intermediate and long-term stability studies on the first three full-scale batches, and to conduct long-term stability studies on a minimum of one marketed production batch per year.

Pharmacovigilance – Risk Management Plan

- In accordance with the new legislation for marketing authorisation applications with regard to the requirement of Risk Management Plan (RMP), the MAH committed to file a variation to add the RMP within 2 months after finalisation of the MRP. This variation has been submitted.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

