IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Clodel 75 mg film-coated tablets
Clopidogrel hydrochloride
PA0711/166/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number DE/H/1840/001 with the DE as RMS. The responsibility of RMS was transferred to Ireland on19 October 2023 under procedure number IE/H/1284/001
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0711/166/001
Marketing Authorisation Holder: Rowex ltd.

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The DE public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMS on quality, safety and efficacy, the RMS considers that the application for Clopidogrel 75mg film coated tablets in the treatment for prevention of atherothrombotic events in the patients specified in the indication section of the SPC is approved.

II. QUALITY ASPECTS

II.1.1 Introduction

The products are formulated as immediate release tablets containing 75 mg clopidogrel HCl. The tablets are packaged in three different container closure systems.

The chemical-pharmaceutical documentation in the dossier is of sufficient quality in view of the present European regulatory requirements.

II.1.2 Drug substance

For the drug substance, clopidogrel HCl, the applicant has submitted an ASMF and additional information from the drug product manufacturer.

The general information about clopidogrel HCl are presented. The synthesis of the drug substance is well described in detail. The intermediate CCSA is manufactured by three plants.

All starting materials, reagents and solvents have sufficient specifications. The carry over of possible impurities in the drug substance has been discussed. Based on this discussion the drug product has presented an acceptable specification for clopidogrel HCl. The specifications based on the relevant ICH guideline (CPMP/ICH/367/96 corr. – Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products).

The analytical methods used in the control of the drug substance have been duly validated according to ICH guidelines.

On basis of the stability data, a retest period has been assigned for clopidogrel HCl. The ASMF holder requires specifying the storage condition.

The closed part of the EDMF is of sufficient quality.

II.1.3 Drug Product

The development of the product has been described, the choice of excipients justified and their functions explained. The excipients are well-known and of Ph. Eur. or NF quality.

The manufacturing process for the Clopidogrel HCl tablets consists of the following processes: manufacture of granules, manufacture of tabletting mixture, manufacture of core tablets and manufacture of coated tablets and packaging.

The validations were performed on industrial batches. The validation results show the process to be sufficiently controlled.

The product specifications cover appropriate parameters of the dosage form.
The analytical methods used in the control of the drug substance have been fully described and validated. Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the release specifications proposed.

The information on the reference standards is adequate.

The information about the packaging materials is adequate.

The conditions used in the stability studies are according to the ICH stability guideline. The drug product control tests and specifications are set adequately. Two alternatively used types of blisters and one HDPE bottle have been tested. For the HDPE bottle an in use stability study has been performed. The stability in the bulk pack has been also tested.

A shelf life of two years without special storage condition are acceptable.

The in use stability and the shelf life for the bulk pack are also acceptable (three and four months, respectively / Do not store above 25°C).

Based on the review of the data on quality, the RMS considers that the application for clopidogrel hydrochloride 75 mg film coated tablets, for prevention of atherothrombotic events,is approvable.

III. NON-CLINICAL ASPECTS

Since this application is a generic application referring to the originator product (Plavix 75mg, film- coated tablets), no new non-clinical studies on the pharmacology, pharmacokinetics and toxicology of clopidogrel have been submitted. Although the product Clopidogrel hydrogenchlorid Sandoz 75 mg differs from the reference medicinal product (Plavix 75 mg, film-coated tablets) with regard to the type of salt, being clopidogrel hydrochloride for Clopidogrel Sandoz 75 mg and clopidogrel hydrogen sulphate for Plavix 75 mg, no additional non-clinical studies have been performed for clopidogrel hydrochloride since hydrochloride is contained in several marketed drug substances and no effects on the pharmacology, pharmacokinetics and toxicology of clopidogrel are expected. The non-clinical overview submitted by the applicant provides a sufficient outline on the available literature concerning the non-clinical pharmacology, pharmacokinetics and toxicology of clopidogrel hydrochloride

IV. CLINICAL ASPECTS

Pharmacokinetics

Clopidogrel is an inactive prodrug *invitro*requiring biotransformation to its active metabolite(s) *invivo*. Clopidogrel is rapidly and extensively metabolised following absorption. SR26334, the inactive carboxylic acid derivative of clopidogrel, is the major metabolite found in the central compartment. Therefore in the past, this metabolite has been used as the marker for the pharmacokinetics of clopidogrel, due to the lack of analytical methods allowing the quantification of clopidogrel in plasma for a sufficient period of time.

Based on measurements of circulating levels of SR26334, it has been inferred that clopidogrel is rapidly absorbed. In recent studies the determination of blood concentration of the parent compound clopidogrel with sensitive detection methods like liquid chromatography tandem mass spectrometry could be achieved. The currently known active metabolite of clopidogrel is a thiol metabolite, which has also recently been indirectly detected and quantified with LC/MS/MS.

The applicant has developed an immediate release formulation of the antiplatelet active drug clopidogrel. The clinical characteristics of this pharmaceutical preparation considering the data available on the Plavix® formulation (Sanofi Pharma) containing an equimolar amount of the active moiety and differing from Plavix® only with regard to the chemical form of the active principle (clopidogrel besilate vs. clopidogrel hydrogen sulphate).

Absorption: The amount of clopidogrel-related metabolites excreted in the urine suggests that absorption of clopidogrel from gastrointestinal tract is at least 50%. Clopidogrel is rapidly absorbed with peak concentration occurring at 1 h after dosing.

Influence of food: In healthy volunteers, absorption of clopidogrel was not significantly affected by the co-ingestion of food or antacids.

Distribution: As demonstrated by *in vitro*studies, the parent compound at concentrations of 0.15 µg/ml and 25 µg/ml is highly bound *(>90%)*to plasma proteins.).

Elimination: Clopidogrel is excreted via the urine and the faeces. While unchanged drug has not been detected in urine, the main identified compounds were SR26334 and glucuronidated metabolites. Renal excretion amounted to 48% and faecal excretion to 46% after multiple dosing.

Metabolism: After oral administration no unchanged clopidogrel was found in urine. Clopidogrel is highly metabolised by hepatic enzymes. The metabolism of clopidogrel and SR26334 is complex and extensive, including hydrolysis, oxidation, dimerisation, and glucuronidation. Studies have shown that the hepatic cytochrome CYP 3A4 and CYP 3A5 might play a predominant role in the bioactivation of clopidogrel in humans was about 8 hours, but radioactivity from labelled clopidogrel had a half-life of about a week, presumably reflecting irreversible binding to platelets by the active metabolite. In a pharmacokinetic study with healthy volunteers receiving either single dose (75 mg) or repeated dose (7 days once daily) of radiolabelled 14C-labeled clopidogrel, the mean cumulative urinary excretion over
120 hours represented 41% of the dose after a single-dose administration and 46 % after administration at steady state. The cumulative faecal recovery over 120 hours ranged from 35 to 60% of single dose and steady state. Mean total excretion of radioactivity was 92% of the dose at single and repeated dose. These data indicate that, following multiple-dose administration of clopidogrel, the biodisposition of the drug remains unaltered compared to a single dose. Information available about the pharmacokinetics of metabolites is limited

Neither racemisation nor decarboxylation to ticlopidine was detected in human studies. PKin specialpopulations

*Impaired renal function:*A multiple-dose study was carried out in subjects with moderate (ClCr 30- 60 ml/min) and severe renal impairment (ClCr 5-15 ml/min) with no controls included in this study. The parent clopidogrel Cmax was higher in severe renal failure patients than in moderate renal failure patients (4.1 vs. 2.7 ng/ml), however, these differences were not statistically significant. Mean AUC and Cmin values of SR26334 appeared to be higher in patients with moderate renal impairment compared to those with severe impairment. There were no significant differences in pharmacodynamic values for the two groups. Renal clearance of SR26334 was proportional to creatinine clearance.

Impaired hepatic function: It has been found that the pharmacokinetic profile of clopidogrel is affected by age and hepatic function. In 12 patients with mild to moderate hepatic impairment (Child-Pugh class A or B) 75 mg clopidogrel once daily for 10 days caused many fold higher mean Cmax values of the parent compound clopidogrel on day 1 and at steady-state on day 10 compared to 12 healthy subjects (111.6 ± 157.5 vs. 1.72 ± 2.0 and 99.7 ± 147.7 vs. 1.9 ± 1.5 ng/ml, respectively). Likewise, the plasma concentrations of the carboxy metabolite SR26334 were higher in cirrhotic patients than in healthy subjects albeit the differences were statistically not significant. In cirrhotics compared to healthy subjects, the AUC values over the dosing interval (AUCτ) for SR26334 were 6.58 ± 2.00 vs. 5.13 ± 0.73 mg h/l on day 1 and 8.28 ± 2.66 vs. 6.39 ± 1.92 mg h/l on day 10. Of note, no differences between both groups were observed in the pharmacodynamic parameters, i.e., inhibition of ADP-induced platelet aggregation and prolongation of bleeding time.

Elderly: In a group of 10 elderly subjects (> 65 years) and in a group of 10 elderly arteriosclerotic patients treated with 75 mg clopidogrel once daily for 10 days, steady-state AUC, Cmax and Cmin values of SR26334 on day 10 were considerable higher compared to those of a group of 10 healthy young subjects (18 - 35 years) indicating a certain degree of accumulation of SR26334 in the elderly population.

Children :Information not available.

Interactions: The bioavailability of clopidogrel is unaffected by food or antacids. Due to extensive metabolism including various hepatic CYP enzymes, Clopidogrel might be subjected to drug interaction with e.g. theophylline, warfarin, phenytoin, ketoconazole and tolbutamide. In-vivo interaction studies demonstrated no interaction with theophylline and digoxin and only minor interaction with oestrogen, cimetidine and pentobarbital. Statins metabolised by CYP 3A might interact with clopidogrel.

Overall the current state of knowledge on PK issues is adequately reflected in the SPC.

Pharmacodynamics

Clopidogrel after bioactivation by metabolising enzymes specifically inhibits P2Y12 receptor, which, in the course of interplatelet signalling, results in an inhibition of platelet aggregation. The maximum inhibitory effect is achieved within 4 to 7 days and persists for 7 to 10 days probably due to an irreversible inhibition of platelet function. However, following a 300 mg loading dose as early as 2 h post dosing a significant effect on platelet aggregation has been observed. Also the bleeding time was significantly prolonged with clopidogrel and reached a maximum of approximately 1.5- to 2-fold of baseline occurring 3 to 7 days after initiation of treatment.

Clopidogrel might interact with warfarin, glycoprotein IIb/IIIa inhibitors, ASA, heparin and other thrombolytics on the pharmacodynamic level due to similar therapeutic principles, e.g. by increasing the risk of bleeding. Since concomitant use of clopidogrel and naproxen increased the incidence of gastrointestinal bleeding, caution is recommended with combination of NSAIDs and clopidogrel. The monitoring of activated partial thromboplastin time (APTT) has been advised on co-medication of clopidogrel with heparin.

The anticoagulation status of patients receiving long-term warfarin therapy was unaffected by concomitant administration of clopidogrel 75 mg daily.Nevertheless concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleedings. Overall, clopidogrel should be used with caution when concomitantly applied with the above-mentioned drugs. Patients receiving clopidogrel should be monitored frequently for bleeding and the physician should be aware of any comedication exerting antiplatelet (e.g. ASA and ticlopidine) or anticoagulant (e.g. warfarin) effects).

Baseline ADP-induced platelet aggregation and also %-inhibition of platelet aggregation by clopidogrel were higher in elderly than in younger subjects indicating increased susceptibility of elderly to platetelet aggregation and clopidogrel treatment. No differences were observed between the three groups in bleeding time. Therefore, dosage adjustment should be considered in elderly subjects.

Despite of different pharmacokinetic parameters the %-inhibition of platelet aggregation and bleeding time prolongation were comparable between healthy subjects and mild to moderate cirrhotic patients. Hence, dose adjustment may not be necessary as these dose levels were well tolerated and found to be safe. However, patients with severe hepatic impairment should not take clopidogrel.

The exact mechanism of clopidogrel resistance is not known properly, but several reasons might contribute to this phenomenon (polymorphism of P2Y12 receptor or metabolising CYP3A4, increased release of ADP or alternate pathways of platelet activation). Patients with ASA resistance might also have an increased disposition for clopidogrel resistance, which is not fully understand currently.

The pharmacodynamic profile of clopidogrel is well known to the scientific community. No additional pharmacodynamic study has been submitted by the Applicant and none is required. All issues outlined above are adequately reflected in the SPC.

Bioequivalence

The bioequivalence of the Test formulation, Clopidogrel hydrochloride film-coated tablet 75 mg (Sandoz PVT Ltd., India)) and the European Reference formulation, Plavix® 75 mg (Clopidogrel hydrogen sulphate) film-coated tablets (Sanofi Pharma Bristol-Myers-Squibb, SNC, France) was compared in a single-centre, open-label, randomised, single-dose, two-period, crossover study in 70 healthy volunteers after informed consent. Both drugs were administered on day 1 as single-dose under fasting conditions. Blood samples (n = 21 per volunteer and period) were drawn pre-dose up to 24 h post dosing according to the sampling schedule specified in the protocol. A washout period of 14 days or more was respected between both treatment periods.

The sampling time points were planned based on the reported pharmacokinetics of the drug. These time points were chosen to assess Cmax, tmax, AUC and t1/2 appropriately. Thus, Test and Reference formulation were administered to healthy volunteers under fasting conditions (at least 10 hours) and blood samples (3 ml each) were taken pre-dose and at 0.167, 0.333; 0.500; 0,667; 0,833; 1.00; 1.25; 1.50; 1,75; 2.00; 2.50; 3.0; 3.50, 4.00; 5.00, 6.00; 8.00; 12.00; 16.00 and 24.00 hours post dose in each period.

Based on these evaluations, comparison of the two formulations of Clopidogrel was carried out. Of the 70 subjects dosed, 67 were included in the statistical analysis, one subject dropped out due to personal reasons (No. 29) and 2 subjects due to adverse events (No. 55 pulse rate increased and No. 69 chest pain). Moreover, terminal half-life and extrapolated AUC (AUC0-∞) is reported only for 64 subjects because elimination rate constant could not properly be estimated.

Safety monitoring was performed at regular intervals during the course of the study. The study was performed between the 19 of January to 03 of February 2008 in Canada.
The analytical quality in regard to pre-study validation was inspected considering the actual FDA Guidance for Industry "Bioanalytical Method Validation" (May 2001) of the Food and Drug Administration and the CPMP "Note for Guidance on the Investigation of Bioavailability and Bioequivalence". From the results of validation it can be concluded that the present analytical method has adequate sensitivity, precision, accuracy, linearity and stability to quantify Clopidogrel in plasma at concentrations that can be expected in real samples. In summary it can be concluded that the analytical method was appropriately validated.

The presented in-study validation data could be classified as complete and plausible and documented in accordance with requirements of FDA Guidance for Industry "Bioanalytical Method Validation" (May
2001) of the Food and Drug Administration. One run of analytical determination of study samples consisted of 8 QCs, 16 calibration curve samples and the samples of three subjects. The results of in-
study validation are documented clearly and fulfilled the acceptance criteria. It can be concluded, that the application of validated bioanalytical method to routine drug analysis was successfully performed.

Study design, analytical methodology and statistical evaluation of the provided bioequivalence study are in accordance with the accepted standards in bioequivalence testing as stated in the EU-Guideline "Note for Guidance on the Investigation of Bioavailability and Bioequivalence".

A comparison of the mean values for AUC0-t, AUC0-∞, Cmax and tmax for the Test and Reference formulation after single-dose administration in fasted state is given below in Table 1.

Table 1: Pharmacokinetic parameters of Clopidogrel following single dose administration of 75 mg of the Test formulation and the Reference formulation Plavix®

Parameters	AUC¥ [pg x h/ml]#		AUC t [pg x h/ml]		C max [pg/ml]		tmax [h]	
	Test	Ref.	Test	Ref.	Test	Ref.	Test	Ref.
N	64#	64#	67	67	67	67	67	67
Mean	1791.58	1926.36	1716.98	1810.90	1272.15	1409.00	0.902	0.871
SD (±)	3051.54	2849.79	2917.00	2754.13	3065.81	3591.25	0.467	0.401
CV (%)	170.33	147.94	169.89	152.09	240.99	254.88	51.81	46.02

3 subjects were excluded because elimination rate constant could not properly be estimated

The mean AUCt for Clopidogrel following administration of the Test and Reference formulation were 1716.98 ± 2917.00 pg · h/ml and 1810.90 ± 2754.13pg · h/ml. Mean AUC∞ were 1791.58 ± 3051.54 pg h/ml and 1926.36 ± 2849.79 pg · h/ml, respectively. Furthermore, the mean tmax was 0.902 ± 0.467 h
and 0.871 ± 0.401 h for the Test and Reference formulation, respectively. The mean Cmax was 1272.15 ± 3591.25 pg/ml following administration of Test and 1409.00 ± 3591.25 pg/ml of Reference product.
The mean residual area was less than 20% for all treatments indicating that a sampling over a period of 24h was sufficient.

The results of the statistical analyses of the relevant parameters for bioequivalence, AUCt, AUC∞ and Cmax, are given in Table 2. Overall, the two formulations were found to be bioequivalent with respect to all relevant pharmacokinetic parameters.

Table 2: Test/Reference ratios and 90% confidence intervals for Clopidogrel following single-dose application under fasted conditions (n = 67)

Endpoint	Test/Reference Ratio	Lower 90% CI	Upper 90% CI	Intra-subject CV(%)
AUCt [pg x h/ml]	95.58	87.11	104.88	33.05
AUC¥ [pg x h/ml]#	94.06	85.43	103.56	33.46

Cmax [pg/ml]	100.87	88.56	114.89	47.54

N = 64

The 90% confidence intervals (CI) of the mean Test/Reference ratios for the primary variables AUCt, AUC∞ and Cmax are within the acceptance range of 80% - 125% stipulated by European guidelines on bioequivalence of immediate release peroral products. The tmax differences for the Test and Reference formulation are insignificant. The widened confidence interval for Cmax proposed in the protocol is therefore of no relevance for the bioequivalence decision. Thus, bioequivalence of Test and Reference formulation is demonstrated with regard to the rate and extent of absorption of Clopidogrel after single- dose administration under fasting conditions.

In conclusion the 90 % confidence interval calculated for AUC0-t, AUC0-∞ and Cmax for Test formulation of Clopidogrel hydrochloride film-coated tablets 75 mg consistently fall within the 80 – 125 % acceptance range after single dose administration. According to the CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) Test and Reference formulation can be considered as bioequivalent Overall, a well designed comparative bioavailability trial employing Clopidogrel hydrochloride film-coated tablets 75 mg as well as the Reference product of Clopidogrel (Plavix®) has been performed. From the results of pre-study validation it can be concluded that the presented analytical method has adequate sensitivity, precision, accuracy, linearity and stability to quantify Clopidogrel in plasma. The documented results of in-study validation demonstrate that the application of validated bioanalytical method to routine drug analysis was successfully performed. The analytical validation procedures and results are in accordance with requirements of relevant FDA "Guidance for Industry: Bioanalytical Method Validation": U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM).

Study design, performance and statistical evaluation of the provided bioequivalence study is in accordance with the accepted standards in bioequivalence testing as stated in the EU-Guideline "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/ QWP/1401/98). The results indicate identical rate and extent of absorption of Clopidogrel from the two formulations tested. Therefore, considering the current European guidelines on bioavailability and bioequivalence, the two formulations tested have identical biopharmaceutical properties. Therefore, it is scientifically justified to assume that all data regarding clinical safety and efficacy available. According to the SPC of the originator (Plavix®), Clopidogrel should be given as a single daily dose of 75 mg with or without food.

Clinical efficacy

The comparison of clopidogrel with ASA in the pivotal phase III study CAPRIE demonstrated efficacy of clopidogrel in reducing a composite outcome of cerebrovascular accident (CVA), myocard infarction (MI), or vascular death with relative risk reduction of 8.7% compared to ASA. In the CURE study the additional administration of clopidogrel to patients treated with ASA led to an efficacious treatment in acute coronary syndrome without ST-segment elevation compared to placebo. The one-year administration of clopidogrel and initiation with a 300 mg loading dose to patients prior to elective PCI proved to be efficacious in the CREDO study. A recent study (CLARITY) with patients receiving fibrinolytic therapy for MI with ST-segment elevation showed favourable results for clopidogrel with significant reduction of primary endpoints (composite of an occluded infarct-related artery or death or recurrent myocardial infarction). In the MATCH study the addition of ASA to an existing clopidogrel therapy did not show an additional value in high-risk patients with TIA or CVA.

Since the CAPRIE study, four large clinical trials have been added to the body of evidence that supports the use of dual antiplatelet therapy in patients with acute coronary syndromes and in those undergoing PCI interventions (CURE, COMMIT, CREDO, CLARITY). However, the recent CHARISMA study only showed a suggestion of benefit with regard to reduction of myocardial infarction, stroke or death from cardiovascular causes when clopidogrel was added to low-dose ASA therapy in patients at high- risk for atherothrombotic events. Considering the subgroup analysis this study showed significant benefit in patients with established vascular disease, but not in those with multiple risk factors and without established cardiovascular disease.

Clopidogrel is recommended as an alternative to aspirin by several guidelines of AHA and ACC. Several studies compared clopidogrel with ticlopidine and demonstrated similar efficacy of both thienopyridines. Nevertheless, clopidogrel showed a more favourable tolerability, which might lead to a better patient compliance, this is further supported by an once daily regimen of clopidogrel in contrast to ticlopidine given twice daily.

It is important to note that sufficient supportive data were available to support the clinical use of clopidogrel in patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

Results of large clinical trials have confirmed the favourable use of clopidogrel in patients suffering from acute coronary syndrome with
- non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing stent placement following percutanous coronary intervention, in combination with ASA, and in
- ST segment elevation acute myocardial infarction, in combination with ASA.

These indications are considered in the SPC of Clopidogrel hydrochloride Sandoz 75 g film coated tablets.

In most of the studies clopidogrel was given as a 75 mg once daily dose. In more recent studies clopidogrel was administered with a loading dose of 300 mg at the beginning, followed by a 75 mg daily dose. Latest studies supported the administration of even a 600 mg loading dose. According to the SPC clopidogrel is intended for a daily dose of 75 mg and in patients with non-ST segment elevation acute coronary syndrome, clopidogrel treatment should be initiated with a single 300 mg loading dose (in combination with 75 to 325 mg ASA, however since higher doses of ASA were associated with an increased bleeding risk a maximum dose of 100 mg ASA is recommended). The clinical trial data reviewed support the use of clopidogrel up to 12 months. In patients with MI with ST segment elevation clopidogrel treatment should be initiated with a single 300 mg loading dose followed by a daily dose of
75 mg (in combination with ASA) with or without thrombolytics.

In patients > 75 years the single 300 mg loading dose is not recommended, however combination treatment should be started as soon as possible after symptoms have occurred and should be maintained for at least 4 weeks.

The current SPC does not give a dosage recommendation for the use of clopidogrel in paediatric patients since there is no experience for this patient group. One published study recommended a dose of 1 mg/kg/day of clopidogrel as starting dose in children.

Clinical safety

The risk of bleeding is the most important adverse effect of clopidogrel, which might be even increased when clopidogrel is concomitantly used with ASA. Therefore, physicians should take bleeding complications into account. If a patient is to undergo elective surgery and an antiplatelet effect is not necessary, clopidogrel should be discontinued 7 days prior to surgery. Other adverse effects are neutropenia, thrombocytopenia, skin rashes and gastrointestinal disorders. Overall, clopidogrel demonstrated a good safety profile.

All relevant safety aspects from clinical trials as well as post-marketing experience of the currently marketed clopidogrel medicinal product are adequately reflected in the SPC.

Overall, it can be deduced that Clopidogrel hydrochloride Sandoz 75 mg film-coated-tablet is safe when used according to the restrictions outlined in the SPC.

Pharmacovigilance System

The applicants have provided documents that set out a detailed description of the Sandoz International GmbH system of pharmacovigilance. A statement signed by Sandoz International GmbH and the Sandoz qualified person for pharmacovigilance, indicating that Sandoz International GmbH has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

For the procedures DE/H/1733+1835+1836+1838+1839+1841/001/DC, the RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume
9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

For the procedure DE/H/1840/001/DC, provided, that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the Member States may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Risk Management Plan

For clopidogrel surveillance routine pharmacovigilance measures are sufficient. Therefore, the MAH's conclusion a RMP being abdicable is endorsed.

Common Renewal Date
A proposed common renewal date of 5 years after finalisation of the procedure was accepted.

Legal Status
Medicinal product subject to medical prescription.

User Testing
As the SPC and PL of this product should be in full accordance with the current product information of the originator product Plavix no user testing is necessary.

V. OVERALL CONCLUSIONS

BENEFIT RISK ASSESSMENT

Study design, analytical methodology and statistical evaluation of the provided relevant bioequivalence study (Study 1) is in accordance with the accepted standards in bioequivalence testing as stated in the EU-Guideline "Note for Guidance on the Investigation of Bioavailability and ioequivalence"(CPMP/EWP/QWP/1401/98).

The 90 % confidence interval calculated for AUC0-t, AUC0-∞ and Cmax for test formulation of Clopidogrel hydrochloride Sandoz 75 mg film coated tablets consistently fall within the 80 – 125 % acceptance range after single dose administration. According to the CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) test and reference formulation can be considered bioequivalent.

All non-clinical and clinical issues discussed during this procedure have been clarified sufficiently, thus it could be concluded that with regard to the confirmed bioequivalence Clopidogrel hydrochloride Sandoz 75mg film-coated tablets thus have a well-recognised efficacy and an acceptable level of safety in the indications approved for Plavix .

The risk-benefit ratio for Clopidogrel hydrochloride Sandoz 75mg film-coated tablets therefore is positive.

The application contains an adequate review of published literature concerning aspects of pharmacology, pharmacodynamic, efficacy and safety of clopidogrel in the clinical overview.

The application is approved. For intermediate amendments, see the current product information.

VI. REVISION DATE

25 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From DE/H/1840/001 to IE/H/1284/001	N/A	19 October 2023	N/A