



European Medicines Agency

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**CHMP ASSESSMENT REPORT**

**FOR**

**Clopidogrel Krka**

International Nonproprietary Name: clopidogrel

**Procedure No. EMEA/H/C/001056**

Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.

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# 1. BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1 Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 25 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Clopidogrel Krka, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – ‘Generic of a Centrally authorised product’.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.  
The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Plavix, 75 mg, film coated tablets
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-07-1998
- Marketing authorisation granted by:
  - **Community**
- Community Marketing authorisation number: EU/1/98/069/001a, EU/1/98/069/001b, EU/1/98/069/002a, EU/1/98/069/002b, EU/1/98/069/003a, EU/1/98/069/003b, EU/1/98/069/004a, EU/1/98/069/004b, EU/1/98/069/005a, EU/1/98/069/005b, EU/1/98/069/006a, EU/1/98/069/006b, EU/1/98/069/007a, EU/1/98/069/007b

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Plavix, 75 mg, film coated tablets
- Marketing authorisation holder: Sanofi Pharma Bristol-Myers Squibb SNC
- Date of authorisation: 15-07-1998
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/98/069/001a, EU/1/98/069/001b, EU/1/98/069/002a, EU/1/98/069/002b, EU/1/98/069/003a, EU/1/98/069/003b, EU/1/98/069/004a, EU/1/98/069/004b, EU/1/98/069/005a, EU/1/98/069/005b, EU/1/98/069/006a, EU/1/98/069/006b, EU/1/98/069/007a, EU/1/98/069/007b
- Member State of source: Germany

The Rapporteur appointed by the CHMP was:  
Pr Philippe Lechat

### Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

### Licensing status:

The product was not licensed in any country at the time of submission of the application.

## 1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 25 July 2008.
- The procedure started on 20 August 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 November 2008.
- During the meeting on 15–18 December 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 December 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 March 2009.
- The summary report of the GCP inspection carried out at a CRO in Canada between 9-12 February 2009 was issued on 07 April 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 May 2009.
- During the CHMP meeting on 26 – 29 May 2009, the CHMP agreed on a List of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of outstanding issues on 03 June 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 11 June 2009. .
- During the meeting on 22-25 June 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Clopidogrel Krka on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 June 2009.

## 2. 2. SCIENTIFIC DISCUSSION

### 2.1 Introduction

Clopidogrel Krka 75 mg film coated tablets is a generic medicinal product containing clopidogrel as clopidogrel hydrochloride as active substance.

The reference medicinal product is Plavix 75 mg film-coated tablets, which contain clopidogrel hydrogensulphate.

Clopidogrel is a non-competitive inhibitor of adenosine diphosphate (ADP) at the platelet receptors. The effect of ADP on platelets is mediated by two G-protein coupled P2Y receptors (P2Y1 and P2Y12) and the cation channel-coupled P2X1 receptor. The adenylate cyclase-coupled ADP receptor P2Y12 is the main target of clopidogrel and lead to inhibition of platelet activation, aggregation, and Gp IIb/IIIa receptor activation. Clopidogrel is a thienopyridine and only the *S*-enantiomer is pharmacologically active.

The safety and efficacy profile of clopidogrel has been demonstrated in several clinical trials details of which can be found in the EPAR for Plavix. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Clopidogrel Krka 75mg film-coated tablet contains clopidogrel hydrochloride. Since this application is a generic application referring to the reference medicinal product Plavix, summary of the clinical data of clopidogrel hydrogensulphate is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with clopidogrel hydrochloride.

The indication for clopidogrel hydrochloride is different from the reference medicinal product. It is part of the indication approved for the reference medicinal product.

The therapeutic indication of Clopidogrel Krka is:

Clopidogrel is indicated in adults for the prevention of atherothrombotic events 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.

The therapeutic indication of Plavix is:

Clopidogrel is indicated in adults for the prevention of atherothrombotic events 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.
- 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.

### 2.2 Quality aspects

#### Introduction

The product is presented as film coated tablets containing 83.5 mg of clopidogrel hydrochloride as active substance corresponding to 75 mg of clopidogrel.

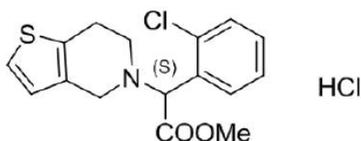
Other ingredients are:

Tablet core: microcrystalline cellulose, colloidal anhydrous silica, crospovidone, macrogol 6000, hydrogenated castor oil

Film coating: hypromellose, titanium dioxide (E171), red iron oxide (E172), talc and propylene glycol  
The film coated tablets are packed in blisters of OPA/Al/PVC-Al.

## Active Substance

Clopidogrel hydrochloride is a white to off-white or yellowish crystalline powder practically insoluble in water at neutral pH but freely soluble at pH = 1. It is also freely dissolves in methanol. Clopidogrel hydrochloride has the chemical name (+)-(S)-Methyl  $\alpha$ -(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate hydrochloride. It does not show polymorphism. The active substance has one chiral centre therefore it exhibits chirality – clopidogrel hydrochloride is synthesized as the S-enantiomer.



- **Manufacture**

Clopidogrel hydrochloride is synthesised by three alternative routes from four key starting materials. The manufacturing process consists of three stages: the synthesis of clopidogrel free base (stage 1), purification of clopidogrel (stage 2) and crystallisation of clopidogrel hydrochloride (stage 3). The active substance is manufactured in two manufacturing sites.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

- **Specification**

The active substance specification includes tests for appearance, solubility (Ph. Eur), identification (IR, chlorides), loss of drying (Ph. Eur), heavy metals (Ph. Eur), sulphated ash (Ph. Eur), related substances (UPLC, HPLC), enantiomeric purity (HPLC), assay (, HPLC), particle size (laser diffraction).

The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitably described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

Batch analysis results (n=16) for active substance manufactured according to all alternative methods by all manufacturers confirm consistency and uniformity.

- **Stability**

.The stability studies have been carried out on three batches of active substance manufactured according to all alternative methods by all manufacturers at long-term conditions (25°C/60 % RH) and at accelerated conditions (40°C/75% RH) packed into drums containing the primary translucent LDPE bag and the secondary laminated bag made of PET/Al/PE foil. Photostability studies have also been carried out.

The stability samples have been stored in a mini-size simulation of the original packing.

Parameters tested during stabilities studies are appearance, loss on drying, related substance, enantiomeric purity, assay and identification.

Clopidogrel hydrochloride is sensitive to basic hydrolysis, oxidation and to acid hydrolysis at elevated temperature. Practically no degradation occurs when clopidogrel hydrochloride is placed at solid state under elevated temperature.

The proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material.

## Medicinal Product

- Pharmaceutical Development

The product has been developed with the objective of developing a conventional release film coated tablet bioequivalent with the reference medicinal product Plavix. It represents an alternative to the reference medicinal product since it contains the same active substance (clopidogrel base) different in the salt (hydrochloride instead of bisulphate) with the same dosage strength and dosage form.

Solubility, particle size and stability of the active substance were taken into consideration during development. A number of studies were also carried out to define the compatibility of the active substance with the pharmaceutical excipients used. A thermoplastic based granulation has been selected as manufacturing process especially in view of safety and environmental issues and it provides good reproducibility and scale-up. The chosen pharmaceutical form, film coating, is necessary especially for taste masking.

The excipients used in the formulation are tablet core: microcrystalline cellulose (diluent), colloidal anhydrous silica (glidant), crospovidone (disintegrant), macrogol 6000 (binder), hydrogenated castor oil (lubricant). Film coating: hypromellose (film coating agent), titanium dioxide (E171) (opacifer), red iron oxide (E172), talc (antiadhesion agent) and propylene glycol (plasticizer). All excipients used are in compliance with the Ph Eur. with the exception of the colouring agent. The methods used for the control of red iron oxide are described. None of the excipients are of human or animal origin.

The film coated tablets are packed in blisters consisting in OPA/Al/PVC film and heat sealing aluminium foil. Supplier statement is provided confirming that the PVC film complies with the PhEur and the aluminium film conforms to the EU Directives.

- Manufacture of the Product

The manufacturing process includes a non-standard thermoplastic granulation. Main steps are mixing, granulation with polymer, sieving, mixing with additives into compression mixture, tableting and film coating.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process on commercial batch size and on both manufacturing sites claimed. The applicant commits to validate the bigger batch size claimed. As the batch size increase do not affect the validation of the non-standard granulation step (increase of sub-batches number) this was accepted.

The batch analysis data show that the film coated tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for appearance, uniformity of dosage (Ph Eur), identification of clopidogrel (HPLC, TLC), identification of titanium dioxide, identification of iron oxides, related substances, enantiomeric purity, dissolution, assay (, HPLC), microbiological purity (Ph Eur) and water content (Ph Eur).

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

Degradation products have been evaluated and found to be acceptable from the point of view of safety.

The tests and limits for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data submitted confirm satisfactory uniformity of the finished product at release.

- Stability of the Product

Three pilot batches of the finished product packed in the intended container were included on stability studies under ICH conditions. The batches were tested for appearance, water, disintegration, hardness, related substances, enantiomeric purity, dissolution of clopidogrel, assay and microbiological tests. They were exposed to 25° C/60% RH for 12 months for and for 6 months at 40°C/75%RH

Photostability tests have been performed in accordance with ICH guideline Q 1 B. Results showed that the tablets became slightly pale and the colour was not homogeneous, which confirms the requirements for the storage of the product in the original package.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

### **Discussion on chemical, and pharmaceutical aspects**

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe

### **2.3 Non-Clinical aspects**

Clopidogrel is widely used well-known substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. This generic application contains a different salt (clopidogrel hydrochloride) of the active substance used in the reference product (clopidogrel hydrogensulphate). A summary of the literature information on non-clinical data of clopidogrel and the results of two new non-clinical studies (acute and chronic toxicity) conducted with clopidogrel hydrochloride were provided. Furthermore, on the basis of the CHMP Guidance for users of the centralised procedure for generic application (EMEA/CHMP/225411/2006), when different salts of the active substance of the reference medicinal product are used, additional information providing proof that their non-clinical safety and/or efficacy profile is not different from that of the reference medicinal product is needed. Thus, information that the different clopidogrel salt (clopidogrel hydrochloride) does not differ significantly in non-clinical properties with regards to safety and efficacy of the reference product were requested by the CHMP in accordance with the relevant guideline.

The response referred to the results of the toxicity and genotoxicity studies to examine the safety profile of clopidogrel hydrochloride vs clopidogrel hydrogen sulphate. The repeated dose toxicity study reports were in accordance with GLP standards and regulatory guidelines (please see section *Toxicology*). The 13-week toxicity study report did not detect major differences in the same safety profile for the hydrochloride and hydrogen sulphate salt; liver was determined as the target organ in both salts. Regarding the genotoxicity testing, clopidogrel hydrochloride tested at a higher concentration level than clopidogrel hydrogen sulphate, turned to be not clastogenic in the chromosome aberration test. In the micronucleus test, at the same dose levels, neither the hydrogen sulphate salt nor the hydrochloride salt was found clastogenic/aneugenic. Thus, based on the data provided, similar safety profile was demonstrated for clopidogrel hydrochloride and clopidogrel hydrogen sulphate.

### **Toxicology**

Two new non-clinical studies were conducted with clopidogrel hydrochloride.

### *Single-dose toxicity*

The acute toxicity study on rats was performed with clopidogrel hydrochloride. Results of single dose toxicity studies in rats revealed low toxicity of clopidogrel hydrochloride at doses 10, 100, 1000 mg/kg. No clinical signs of toxicity and mortality were reported in rats after the administration of drug. No significant differences in body weight gain were seen between the control and treated groups. At terminal necropsy, no apparent macroscopic changes attributed to clopidogrel hydrochloride administration were observed in any animal. The majority of tissue was macroscopically unremarkable. LD<sub>50</sub> values were over 1500mg /kg for both sexes.

After a single oral administration of clopidogrel in mice, rats and baboons, toxicity occurred only at very high doses and the target organs were mainly the gastrointestinal tract, the kidney and the lung. The oral LD<sub>50</sub> values of clopidogrel were over 2 g/kg in all species.

### *Repeated-dose toxicity*

The toxicity of clopidogrel hydrochloride was investigated in rats upon daily oral administration by gastric gavage for 13 consecutive weeks. The study was conducted with four groups of 10 males and 10 females each versus one vehicle control group and 3 test groups receiving 12.5, 125 or 250 mg/kg body weight/day. Treatment with clopidogrel hydrochloride was generally well tolerated, based on the lack of treatment related clinical signs and the normal growth of the animals. Some treatment related changes in haematology, e.g. thrombocytes, and clinical chemistry, e.g. cholesterol, triglycerides, bilirubin, total protein, etc., were revealed. Decreased thymus weights, increased adrenal, kidney, seminal vesicles and liver weights and hypertrophy of centrilobular hepatocytes were also observed. The no-observed-adverse-effect level (NOAEL) for clopidogrel hydrochloride was considered 12.5 mg/kg body weight/day. There appears to be no additional toxic effects of clopidogrel hydrochloride although no direct comparative data between the clopidogrel hydrochloride and clopidogrel hydrogensulphate were provided. Furthermore, any potential differences in the non-clinical toxicokinetic profile would be apparent in the clinical pharmacokinetic profile addressed by the bioequivalence studies.

### *Genotoxicity*

The *in vitro* *Salmonella typhimurium* reverse mutation assays of clopidogrel hydrochloride was performed and revealed evidence that clopidogrel did not induce effects at either the gene or chromosome levels. In Ames test of clopidogrel's main metabolite S-carboxylic acid derivative was also negative. The eventual mutagenic activity of clopidogrel hydrochloride was investigated in the bacterial reverse mutation assay with *Salmonella typhimurium* strains TA97a, TA98, TA100, TA 1535 and TA102, without and with metabolic activation. The tested substance was considered non mutagenic. Clopidogrel was not genotoxic in micronucleus test in mice. Incidence of micronucleated polychromatic red blood cells (RBCs) was not elevated in mice received clopidogrel at oral doses up to 2000 mg/kg daily, for three consecutive days. Ratio of polychromatic to normochromatic RBCs was also normal which indicates that there was no bone marrow cytotoxicity. There was no evidence of any clastogenic activity for clopidogrel.

Although the *in vitro* studies did not reveal any mutagenic, genotoxic or clastogenic potential of clopidogrel, the CHMP raised a major objection with respect to the studies on impurities, which did not follow recommendations of the OECD guideline, protocol 471 (*OECD, 1997, Test Guideline 47: Bacterial Reverse Mutation Test. In: OECD Guideline for Testing of Chemicals. Paris, Organization for Economic Cooperation & Development*) and of the *Question & Answers on the CHMP guideline on the limits of genotoxic impurities* (EMA/CHMP/SWP/431994/2007). In response, adequately conducted reverse mutation assays in accordance with GLP standards and OECD guideline protocol number 471 was provided. The results of the Ames test performed with potassium ethyl sulphate and clopidogrel isopropyl sulphate indicated that these two substances do not hold a mutagenic potential. Thus, the content limit for monoalkylsulphates as proposed by the applicant is acceptable to the CHMP.

Introduction of the product onto the market is unlikely to result in any significant increase in the combined sales volumes for all clopidogrel hydrogensulphate products, and would thus not be expected to have an adverse effect upon the environment. With this regard and on the basis of CHMP Guideline

on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00), a formal environmental risk assessment is not considered necessary.

## 2.4 Clinical Aspects

### Introduction

The CHMP assessment addressed pharmacokinetic data in respect of one bioequivalence study.

### GCP

The bioequivalence study provided in support of the application was performed by CROs in Canada. A statement was provided that the clinical part of these studies was conducted according to the ICH Note for Guidance on Good Clinical Practices.

During the evaluation of the dossier, the CHMP considered that in the view of the reported discrepancies that occurred during clopidogrel plasma analysis, it was necessary to inspect the conduct of the bioequivalence study 07-197. The results of this triggered inspection and the satisfactory responses to its findings are an integral part of the procedure.

### Clinical studies

One bioequivalence study comparing Clopidogrel Krka 75 mg film coated tablets with the originator Plavix 75 mg film-coated tablets was provided. The study was performed in fasting subjects and measured the parent drug and the major (inactive) metabolite, clopidogrel carboxylic acid. In addition, this generic product contains a different salt of clopidogrel (clopidogrel hydrochloride) in comparison with the reference medicinal product. Thus, the CHMP raised a major concern, since on the basis of the CHMP Guidance for users of the centralised procedure for generic application (EMA/CHMP/225411/2006), when different salts of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from that of the reference medicinal product is needed.

### Pharmacokinetics

- Methods

#### STUDY DESIGN

*Study code: 07-197*

*Comparative, randomised, single-dose, 2-way crossover bioavailability study of clopidogrel 75 mg film-coated tablets (test) and Plavix 75 mg film-coated tablets (reference) in healthy adult male volunteers under fasting conditions*

The objective of this study was to assess the single-dose relative bioavailability of clopidogrel 75 mg film-coated tablets (KRKA, d.d.) and Plavix 75 mg clopidogrel film-coated tablets (Sanofi-Synthelabo Limited), under fasting conditions. This was an open-label, randomised, single-dose, 2-way crossover, 2-sequence, comparative bioavailability study performed on volunteers. A total of 92 subjects completed the clinical phase of the study. Single oral 75 mg clopidogrel doses were separated by a washout period of 14 days. The protocol and informed consent forms (ICFs) were reviewed and approved by an Institutional Review Board (IRB) convening the CRO in October and November 2007. The study was conducted between 1 December and 22 December 2007.

#### TEST AND REFERENCE PRODUCTS

Clopidogrel 75 mg film-coated tablets, manufactured by KRKA, d.d. Novo Mesto, Slovenia, batch 1232 01 I068 1007.

Plavix 75 mg tablets manufactured by Sanofi-Synthelabo, United-Kingdom, batch 600711.

## POPULATION(S) STUDIED

A total of 96 healthy, non-smoking, adult male volunteers aged 18-55 years and with BMI 18.00 – 28.00 kg/m<sup>2</sup> were included in the study. These were medically healthy subjects with clinically normal laboratory profiles, vital signs and ECGs. Of the 96 subjects, 4 subjects were withdrawn or discontinued. 92 subjects finished the study and were included in the analysis. Adequate inclusion and exclusion criteria were followed. The choice of the selected population in this clinical trial was considered appropriate.

## ANALYTICAL METHODS

The plasma samples were assayed for clopidogrel and its carboxylic acid metabolite using LC/MS/MS method. The analytical technique was initially validated at a CRO in Canada, and transferred afterward to another CRO in Canada. A partial validation was conducted successfully in order to allow this transfer. However, there were insufficient data submitted with respect to the pre-study validation and validation of the bio-analytical technique used for determination of clopidogrel, and the CHMP questioned the validity of the bioequivalence study. Thus, a GCP inspection was requested.

## PHARMACOKINETIC VARIABLES

The primary pharmacokinetic parameters defined in the protocol were AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and maximal plasma clopidogrel concentration C<sub>max</sub>.

## STATISTICAL METHODS

Analysis of variance (ANOVA) was carried out on ln-transformed AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> for both analytes: clopidogrel and the main inactive metabolite. A non-parametric test was carried out to compare the T<sub>max</sub> values between treatments. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as random effect. The statistical methods used were acceptable.

- Results

Pharmacokinetic parameters for clopidogrel (AUC and C<sub>max</sub>: arithmetic mean ± SD, t<sub>max</sub>: median, range) following a single 75 mg oral dose (n=92) in study 07-197 are presented below.

<b>Treatment</b>	<b>AUC<sub>0-t</sub></b> pg*h/ml	<b>AUC<sub>0-∞</sub></b> pg*h/ml	<b>C<sub>max</sub></b> pg/ml	<b>t<sub>max</sub></b> h
<b>Test</b> <b>(S.D.)</b>	2257.6 (3482.8)	2579.1 (3891.4)	1106.7 (873.3)	1 (0.33-16)
<b>Reference</b> <b>(S.D.)</b>	1909.7 (1575.7)	1983.4 (1649.5)	981.4 (1001)	1 (0.33-5)
<b>*Ratio (90% CI)</b>	[90;110]%	[87; 109]%	[84;108]%	
<b>Point estimate</b>	100 %	98 %	95 %	
<b>Intra-subject CV (%)</b>	43.3 %	43.5 %	54.6 %	
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>T<sub>max</sub></b> time for maximum concentration : median, min and max				

*\*log-transformed values*

Pharmacokinetic parameters for clopidogrel carboxylic acid (AUC and C<sub>max</sub>: arithmetic mean ± SD, t<sub>max</sub>: median, range) following a single 75 mg oral dose (n=92) in study 07-197 are presented below.

Treatment	AUC <sub>0-t</sub> ng*h/ml	AUC <sub>0-∞</sub> ng*h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h
<b>Test (S.D.)</b>	6632.4 (1372.7)	7105.8 (1452.4)	2545.7 (873.3)	0.685 (0.5-3)
<b>Reference (S.D.)</b>	6674.7 (1435.9)	7229.6 (1536.3)	2608.9 (854.9)	0.775 (1-5)
<b>*Ratio (90% CI)</b>	[96;100]%	[97; 100]%	[91;104]%	
<b>Point estimate</b>	98 %	98 %	97 %	
<b>Intra-subject CV (%)</b>	8.4 %	7.8 %	26 %	
AUC <sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity AUC <sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours C <sub>max</sub> maximum plasma concentration T <sub>max</sub> time for maximum concentration : mediane, min and max				

*\*log-transformed values*

The following acceptance criteria were set as per clinical study report:

- The 90% confidence interval for the exponential of the difference between the test and the reference product for the ln-transformed parameters AUC<sub>0-t</sub> and AUC<sub>inf</sub> should be within **80-125%**.
- The 90% confidence interval for the exponential of the difference between the test and the reference product for the ln-transformed parameter C<sub>max</sub> should be within **75-133%**.

The proposed 90% confidence intervals for AUC<sub>t</sub> and AUC<sub>inf</sub> are in line with the recommendation of the CHMP guideline CPMP/EWP/QWP/1401/98 Rev.1 and the observed results of the clinical study fulfil this requirement. However, the widening of the limits for bioequivalence conclusions for C<sub>max</sub> values, although not in line with the current CHMP recommendations, was not considered necessary since the C<sub>max</sub> results of the study are within the standard 80-125% limits required by the NfG on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98. No significant difference in T<sub>max</sub> was evidenced by the non parametric test.

No serious adverse events (SAEs) were reported during this study. Overall, clopidogrel demonstrated a good safety profile. The risk of bleeding is the most important adverse effect of clopidogrel, which might be even increased when clopidogrel is concomitantly used with ASA. No significant changes in the subjects' state of health were observed and it is believed that Clopidogrel Krka 75 mg film coated tablet is safe when used according to the SmPC.

From the 96 subjects included in the study, four were withdrawn for personal reasons or non-compliance. 92 subjects finished the study and were included in the data set for statistical analysis. All withdrawn and discontinued subjects are documented and validity is justified.

#### ▪ Conclusions

Based on the presented bioequivalence study 07-197, Clopidogrel Krka is considered bioequivalent with Plavix.

#### Pharmacodynamics

No studies were submitted.

#### Post marketing experience

There was no post-marketing data submitted by the Applicant for this product.  
There is a wide postmarketing experience with clopidogrel.

## 2.5 Pharmacovigilance

### ▪ PSUR

The PSUR submission schedule for Clopidogrel Krka should follow the PSUR submission schedule of the reference medicinal product.

### ▪ Description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

### ▪ Risk Management Plan

Risk Management Plan has not been submitted. Since the application concerns generics of respective reference medicinal products for which no safety concerns requiring additional risk minimization activities have been identified, this considered acceptable.

### Discussion on Clinical aspects

One clinical bioequivalence trial 07-197 was provided for Clopidogrel Krka application, analysing the parent prodrug clopidogrel. The demonstration of the unchanged safety/efficacy profile of clopidogrel hydrochloride when compared with Plavix (clopidogrel hydrogensulphate) was raised by the CHMP as a major issue for this generic product. In response, further discussion on the comparability of the efficacy and safety profiles of clopidogrel hydrogen sulphate and clopidogrel hydrochloride was provided. Pharmacokinetics, dissolution, adverse events profile and other clinical data were considered and it was concluded that the two salts of clopidogrel have a comparable safety/efficacy profile.

At the time of approval of the reference product Plavix, there was no reliable and validated methodology for the determination of the pharmacokinetics of the parent prodrug clopidogrel, or of the active metabolite clopidogrel thiol. Thus, the pharmacokinetic profile was established based on the pharmacokinetics of clopidogrel carboxylic acid, which is the non-active metabolite. In the meantime, a reliable bioanalytical method for determination of clopidogrel in plasma and urine was developed. Since the pharmacokinetic profile of the active metabolite is still not well established, the CHMP accepted the proof of bioequivalence based on the clopidogrel parent compound data in study 07-197. Thus, data related to pharmacokinetics of clopidogrel carboxylic acid are considered supportive, whereas data on clopidogrel parent drug is important for the confirmation of bioequivalence.

The indication of Clopidogrel Krka is different from that of the reference medicinal product, Plavix (please see section 2.1). Thus, the Product Information has been adequately amended to reflect this change and this is considered acceptable.

Furthermore, the recently published literature data indicate that the bioavailability of a single oral dose of clopidogrel and the pharmacokinetic parameters of clopidogrel, especially  $C_{max}$  and  $AUC_{inf}$ , might be increased by several folds in the fed condition compared to the fasted condition. The currently presented clinical studies were conducted in fasted state and thus, the CHMP requested a clarification of this approach and adequate justification why bioequivalence for the generic product should be demonstrated only under fasting condition was provided. Bioequivalence studies in fasting conditions are normally recommended as mentioned in the Questions & Answers on the Bioavailability and Bioequivalence Guideline (EMA/CHMP/EWP/40326/2006) document as the drug product is to be administered under fasting as well as fed conditions. In addition to the dissolution studies using clopidogrel hydrogen sulphate, conducted at three different pH values (1.2, 4.5, 6.8), the applicant provided an additional in vivo bioequivalence study conducted under fed conditions. The comparative in vitro dissolution studies under conditions mimicking the fed state as well the fed state

bioequivalence study did not reveal any major differences when compared to the reference drug product.

The bio-analytical technique and methodology applied in the analysis of the samples during the bioequivalence studies included validation with the analysis of calibration curves and controls at various concentrations. The CHMP questioned whether there is a potential for back-conversion of the quantitatively major metabolite clopidogrel carboxylic acid to the parent drug. Considering that the plasma levels of clopidogrel carboxylic acid are considerably higher than those of the parent drug, a minimum back-conversion of the metabolite would lead to a significant over-estimation of clopidogrel plasma levels and would bias the outcome of the bioequivalence study. The back-conversion could occur in the presence of alcohol used in sample preparation and analysis. It was, indeed, reported that a possible back-conversion of clopidogrel metabolite to clopidogrel parent drug was evidenced in the presence of methanol. In order to avoid this process, the extraction procedure was changed and methanol-free conditions employed. Although it has been indicated that stability tests were performed in order to prove the reproducibility and accuracy of clopidogrel concentration measurements, the CHMP questioned these results since no clear description of the analytical technique including extraction procedure actually used in the initial pre-study validation process was provided. Information on the validation procedures in study 07-197 was requested by the CHMP. In response, details of the bio-analytical methodology and full validation details were provided demonstrating that no methanol, which is needed for the conversion the acid metabolite to clopidogrel, was used and thus, no source of methylation exists within the entire methodology, including all solution preparation, plasma sample processing, handling storage and LC-MS/MS determination. The CHMP considered this issue resolved.

Considering the above difficulties in the determination of clopidogrel in plasma especially the issue related to the possible back-conversion of the metabolite to the parent drug, a triggered GCP inspection of the bioequivalence study was requested by the CHMP, which was of the opinion that results of this inspection and the satisfactory responses to its findings were an integral part of the evaluation procedure. The inspection identified major and minor findings that seem not to affect the overall results of the trial.

The bioequivalence study 07-197 and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). The parameters used to establish bioavailability included the area under the plasma concentration-time curve and the maximal plasma concentration of the parent compound of clopidogrel. The 90% confidence intervals for these parameters were within the recommended 80-125% range for clopidogrel, required by the above mentioned guideline. The proposed widening of the 90% confidence interval for clopidogrel  $C_{max}$  to 75%-133% was found to be unacceptable by the CHMP; nevertheless, since the confidence intervals for  $C_{max}$  values of clopidogrel were within the required 80-125% range, the need for widening of the intervals was not applicable. The bioequivalence with Plavix was proven.

- User consultation

The results of user consultation provided indicates that the Package leaflet is well structured and organized, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable in patients /users are able to act upon the information that it contains.

## **2.6 Overall conclusions, benefit/risk assessment and recommendation**

### **Overall conclusion and Benefit/risk assessment**

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/Risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

### **Recommendation**

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Clopidogrel Krka in the prevention of atherothrombotic events 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.

was favourable and therefore recommended the granting of the marketing authorisation.