European Medicines Agency

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WITHDRAWAL ASSESSMENT REPORT FOR

CLOPIDOGREL TEVA PHARMA

International Nonproprietary Name: clopidogrel
Procedure No. EMEA/H/C/1052

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP List of Questions, the Rapporteur considers that the application for Clopidogrel Teva Pharma 75mg film-coated tablets (clopidogrel as clopidogrel hydrobromide) indicated 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.
(Indication is not the same as at the begining of the procedure).

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Proposal for Questions to be posed to additional Experts

None.

Inspection issues

None.

II. EXECUTIVE SUMMARY

II.1 Administrative information

This Day 180 List of Questions (LoQ) is based on the Day 150 Assessement Report and the subsequent comments from the Member States.

II.2 Quality aspects

The information on the drug substance is presented in the form of an ASMF- Active Substance Master File. Outstanding issues over the confidential (closed) part of the ASMF have been identified. These concerns will not be revealed to the MA Applicant, they will be conveyed in confidence to the holder of the ASMF. The response of the ASMF holder should be coordinated to arrive at approximately the same time as the responses from the MA Applicant.

Active substance:
The active substance is a different salt of clopidogrel (hydrobromide) compared to the reference product (hydrogen sulphate).
Details of manufacturers have been included. Two alternates in synthesis are presented. The route of synthesis was evaluated for presence of possible genotoxic impurities. The drug substance shows polymorphism. Further evidence that the chosen polymorphic form is stable and that other polymorphic forms could not be formed during the manufacturing procedure remains to be demonstrated.
As there is no monograph of clopidogrel hydrobromide in the Ph. Eur., Teva developed its own specifications and test methods for the quality control. In the specifications there are all relevant parameters and they are considered acceptable. The analytical procedures are, except the XRPD method for polymorph identification, suitable validated.
Stability studies in accordance with the relevant ICH/CHMP guideline have been performed. 12 months stability data on two production batches of clopidogrel HBr at storage conditions 2 – 8 °C and 25 °C/60 % RH are provided. No result of the tested parameters was found to be outside the specification limits.

Medicinal product:
The pharmaceutical form is a film-coated tablet. It has been developed as a generic equivalent to Plavix film-coated tablets from Sanofi Pharma Bristol-Myers Squibb. The excipients used are Ph. Eur. substances regularly used in tablet manufacture. Dissolution and impurity profile data indicate that Teva's tablets are comparable to the reference product. The discriminating power of the dissolution method was demonstrated. Details of finished product manufacturers (including manufacturers of the dosage form, primary packaging, secondary packaging, QC testing and batch release sites) have been included. The manufacturing process is a standard one for film-coated tablets. It is sufficiently documented.
The specifications of the finished product and the in-process controls cover all essential quality aspects required for film-coated tablets by the Ph. Eur. and the applicable ICH/CHMP guidelines.
The specification limits proposed for one of the specified impurities remain to be further justified by toxicological data or qualification otherwise demonstrated and the shelf life limit should be proposed taking into account the limit for this impurity in drug substance, in drug product at release and the results of the stability study where no increase of this impurity was observed. The analytical procedures are validated. The quality of the drug product outlined in the batch data is acceptable.
The stability studies have been conducted in accordance with the relevant ICH/CHMP guideline and 15 months stability data were provided. As the content of one specified impurity increases with temperature, the storage conditions regarding temperature are »do not store above 25 °C«. This consideration was correctly reflected in SPC, package leaflet and labeling. Different shelf-lives for the blister pack and HDPE bottle presentations were assigned according to the accumulated stability data submitted.

In summary, there were no major objections related to quality at Day180 of the procedure. The minor objections that have not been satisfactorily clarified at the time of withdrawal are briefly outlined above, and there were also some other minor unresolved quality issues related to the confidential part of the Active Substance Master File.

II.3 Non clinical aspects

The Applicant used a different salt of clopidogrel (clopidogrel hydrobromide) compared to the reference product.

The applicant provided a review of the non-clinical data of clopidogrel. Clopidogrel is widely used and it is a well-known substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised, therefore the applicant has not provided additional studies. The excipients used in drug formulation are conventional, well known and broadly used in other medicinal products.

Since the product contains a different salt of active substance, the applicant provided justification that different salt, used in the product, does not differ significantly in properties with regards to safety and efficacy of the product, which is in accordance with EMEA Guidance for users of the centralised procedure for generic application (EMEA/CHMP/225411/2006).
The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology, based on literature data, is thus adequate for approval.

Pharmacology

The antiaggregating activity was evaluated in *ex vivo* and *in vitro* models. Oral and intravenous administration of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. The active metabolite responsible for the activity of the drug has been isolated recently. The action of clopidogrel is irreversible due to the modification of the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the rest of their lifespan

and this effect is of a special pharmacological importance. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by the released ADP. Clopidogrel does not inhibit phosphodiesterase activity.
Safety pharmacology studies did not reveal any relevant effects on the central nervous, cardiovascular, respiratory, gastrointestinal and renal systems.

Pharmacokinetics

Pharmacokinetic studies preformed in laboratory animals and published in the literature revealed that clopidogrel is rapidly absorbed after oral administration. Oral bioavailability is at least 50%. Clopidogrel and its main circulating metabolite bind reversibly to plasma proteins. Clopidogrel is rapidly and extensively distributed in the body; in animal studies it was demonstrated to cross blood placenta barrier. It is distributed into the milk of lactating rats..
The metabolism is hepatic; extensive and rapid, by hydrolysis to the main circulating metabolite, the carboxylic acid derivative, which accounts for approximately 85% of the circulating compounds. A glucuronic acid conjugate of the carboxylic acid metabolite has also been found in plasma and urine. Neither the parent compound nor the carboxylic acid derivative has a platelet inhibiting effect.
The elimination is renal, approximately 50% of the dose is excreted within five days after dosing with radiolabeled clopidogrel; and fecal, approximately 46% of the dose is excreted within five days after dosing with radiolabeled clopidogrel.

Toxicology

Single-dose toxicity
Acute oral LD_{50} in mice, rats and baboons exceeded 200 mg/kg, acute i.v. LD_{50} was 110-160 mg/kg. Target organs of single dose oral toxicity were digestive tract (erosions, haemorrhage), lung (congestion) and kidneys (necrotic tubulopathy); target of i.v. toxicity was cardio-respiratory (rapid death after cyanosis, dyspnea, apnea).

Repeated-dose toxicity
After one year of administration of clopidogrel base (affording up to 123 mg/kg) to rats no excess of treatment related mortality was observed. At the end of the treatment, plasma cholesterol levels were elevated up to 19 and 42 % in high dose group of males and females respectively. Liver weight in high dose groups was also increased by approx. 20%, reflecting the hypertrophy of centriobular hepatocytes seen at microscopy.
After one year treatment with up to 200 mg/kg clopidogrel to baboons no excess of treatment related mortality was observed. Other effects observed were: reduced body weight gain, high dose reduction in RBC count and haemoglobin, urine pH, and ca. 30% increase of liver weight. All changes had reversed at the end of a 5-week recovery period.

Genotoxicity
Genotoxicity tests were preceded to identify cytotoxic concentration. Ames tests were performed on clopidogrel, its major metabolite, the R-enantiomer metabolite. Results for clopidogrel were uniformly negative, both in the presence and absence of rat hepatic metabolic enzymes.
Clopidogrel was not genotoxic in three other *in vitro* tests (DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Carcinogenicity
Standard 18 and 24 month carcinogenicity assays were preformed with Clopidogrel 75mg tablets in mice and rats, at up to 77 mg/kg base. No evidence of carcinogenicity was revealed.

Reproductive toxicity
Effects of clopidogrel on reproductive function and on peri- and post-natal development were investigated in four studies in rats and rabbits covering all three reproduction segments, including both male and female fertility, teratogenicity and any next generation carry over effect. The dose was chosen on the basis of maternal or paternal toxicity in preliminary studies. No effects on fertility and

mating performance of males or females were recorded. No abnormal effects on fertility or mating performance of F1 generation, on survival and development of F2 pups up to weaning were seen. The only remarkable effect observed was a reversible retardation of F1 neonatal growth. Clopidogrel was not teratogenic at up to 500 mg/kg, and exposure *in utero* to this parental dosage did not affect F1 development and fertility.

Environmental Risk Assessment
Introduction of the product onto the market is unlikely to result in any significant increase in the combined sales volumes for all clopidorel containing products, and would thus not be expected to have an adverse effect upon the environment. With this regard and on the basis of EMEA Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00) a formal environmental risk assessment is not considered to be necessary.

II.4 Clinical aspects:

Pharmacokinetics

To support the application, the applicant has conducted two bioequivalence studies comparing Clopidogrel Teva 75 mg film-coated tablets (clopidogrel hydrobromide as active substance) with the originator Plavix 75 mg film-coated tablets, Sanofi-Synthelabo Ltd., from the French market (clopidogrel hydrogen sulphate as active substance). Both studies were performed in fasting subjects, one involved measuring the parent drug and another involved measuring the major (inactive) metabolite, clopidogrel acid. Furthermore, the applicant has conducted one pharmacokinetic study with Plavix 75 mg film-coated tablets, Sanofi-Synthelabo Ltd, UK, in order to estimate the intra-subject variability of the pharmacokinetic parameters AUC_t, $AUCi_{nf}$ and C_{max} of Plavix 75 mg tablets under fasting conditions.

Study code: 2008-1695 (single dose under fasting conditions)
This was an open-label, randomised, single-dose, two-period, two-sequence, two-treatment, crossover study performed on 120 healthy males and female volunteers using a 75 mg single dose. Blood samples were collected 16 hours for the analyses of clopidogrel HBr. 117 subjects (males and females) completed the study and their data are included in the statistical analysis. Drop outs handling was performed according to the protocol requirements. The protocol deviations were not considered to have an impact on the efficacy and safety evaluation.

The primary pharmacokinetics parameters investigated were AUC_t, AUC_{inf} and C_{max}.

The proposed 90% confidence interval criteria of the relative mean measured parameters of clopidogrel bioequivalence of test / reference were: AUC_t and AUC_{inf} 80-125% and C_{max} 75-133%.
The proposed acceptance criteria of 75-133% for C_{max} could not be accepted based solely on PK data. Bioequivalence with regard to the rate of absorption of clopidogrel has not been demonstrated between the test and reference tablet in this study.

The raised points relating to higher extrapolated AUC and T_{max} observed in the first sample time have been satisfactory solved.

Study code: 2008-1641 (single dose under fasting conditions)
This was an open-label, randomised, single-dose, two-period, two-sequence, two-treatment, crossover study performed on 24 healthy males and females volunteers using a 75 mg single dose. Blood samples were collected 36 hours for the analyses of clopidogrel acid. 23 subjects (males and females) completed the study and data of 23 subjects included in the statistical analysis. Drop outs handling was performed according to the protocol requirements. The protocol deviations were not considered to have an impact on the efficacy and safety evaluation.

The primary pharmacokinetics parameters investigated were AUC_t, AUC_{inf} and C_{max}.

The calculated 90% CIs for ln-transformed AUC_t, AUC_{inf} and C_{max} fell within the acceptance range of 80-125%. The calculated intra-subject variability was reasonably low for metabolite, clopidogrel acid.

Study Code: 2008-1706 (Plavix vs Plavix)
This was an open-label, single-dose, two-period, single-treatment cross-over study, performed on 18 healthy males and females volunteers using a 75 mg single dose under fasting conditions. Blood samples were collected 16 hours for the analyses of clopidogrel bisulphate. 16 subjects (males and females) completed the study and were included in the statistical analysis. Drop outs handling was performed according to the protocol requirements. The protocol deviations were not considered to have an impact on the efficacy and safety evaluation.

The primary pharmacokinetics parameters investigated were AUC_t, AUC_{inf} and C_{max}.

In this study Plavix showed an intra-subject variability of >30%. Although these data indicate high within-subject variability, it has not been established that clopidogrel is a "highly variable" drug.

Bioanalytical method
The plasma samples were assayed for clopidogrel and its metabolite using LC/MS/MS method. The analytical method has been sufficiently validated by a Clinical Research Organisation in Canada. Adequate long-term stability data are presented for both clopidogel and clopidogrel acid.

Conclusion on the bioequivalence studies
The bioequivalence study and statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Note for Guidance (CPMP/EWP/QWP/1401/98). The parameters used to evaluate bioavailability included AUC and C_{max} of the parent compound of clopidogrel and its inactive metabolite. The calculated 90% CIs for ln-transformed AUC_t, AUC_{inf} and C_{max} fell within the acceptance range of 80-125% for both the parent drug clopidogrel and clopidogrel acid inactive metabolite but fell outside of the acceptance range for C_{max} of clopidogrel.
The applicant has adequately justified the major objection relating to demonstration of bioequivalence based on parent compound only. There remain two major concerns regarding the non-acceptance range for C_{max} and regarding the use of an alternative salt (HBr) as a substitution for bisulphate, since further information on the safety and efficacy of clopidogrel hydrobromide is needed. The bioequivalence has not been demonstrated.

A final decision on the approvability of the applied product will be possible when satisfactory responses are given to the CHMP List of Outstanding Issues.

Pharmacodynamics
Not applicable

Clinical safety
Not applicable

Post marketing experience
Not applicable

Pharmacovigilance system

The applicant submited a detailed description of the pharmacovigilance system in accordance with the Volume 9A and "The guideline on monitoring of compliance with Pharmacovigilance regulatory obligations and Pharmacovigilance inspections".
The PSUR submission schedule for Clopidogrel Teva Pharma 75mg film-coated tablets should follow PSUR submission schedule for Plavix 75 mg film-coated tablets. The schedule should be specified before the finalisation of the procedure. The rapporteur for Clopidogrel Teva Pharma 75mg film-coated tablets, who will surveill pharmacovigilance according to the drafted generics/hybrid

applications guideline will be the rapporteur of the centrally authorised originator product Plavix 75 mg film-coated tablets.

Risk Management plan

A risk Management Plan has not been submitted. Since this application concerns a generic of a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified, a Risk Management Plan is not required.