18 December 2014
EMA/63392/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Clopidogrel ratiopharm

International non-proprietary name: clopidogrel

Procedure No. EMEA/H/C/004006/0000

Note

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 Teva Pharma B.V. submitted on 2 July 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Clopidogrel ratiopharm, through the centralised Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on procedure under 25/04/2014.

The application concerns a generic medicinal product as defined in Article 10(2) (b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Prevention of atherothrombotic events

Clopidogrel is indicated in:

• Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

• Adult patients suffering from acute coronary syndrome:

– Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).

– ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Plavix instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with

authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

This application is submitted as a multiple of Clopidogrel Teva authorised on 28 July 2009 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The submission of this application is due to patent grounds.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions 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 Clir SNC
  - Date of authorisation: 15-07-1998
  - Marketing authorisation granted by:
  - Community Marketing authorisation numbers: EU/1/98/069/001-011
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Plavix 75 mg film-coated tablets
  - Marketing authorisation holder: Sanofi Clir SNC
  - Date of authorisation: 15-07-1998
  - Marketing authorisation granted by:
  - Community Marketing authorisation numbers: EU/1/98/069/001-011

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 Clir SNC
- Date of authorisation: 15-07-1998
- Marketing authorisation granted by:
  - Member State (EEA) : United Kingdom
  - (Community) Marketing authorisation numbers: EU/1/98/069/001-011

Bioavailability study number(s): Protocol No.:2007-1362 version 2 and Protocol No.: 2008-1676

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Clopidogrel ratiopharm has been given a Marketing Authorisation in Canada on 14 March 2007, in Hong Kong on 1 September 2009, in Israel on 31 January 2008, in Russia on 24 February 2011, in Taiwan on 18 December 2012, in Vietnam on 8 February 2011, in the United States on 17 May 2012, in Brazil on 9 February 2011, in South Africa on 14 June 2013, in Turkey on 31 March 2009 and in Ukraine on 16 October 2012.

1.2. Manufacturers

Manufacturers responsible for batch release

TEVA Pharmaceutical Works Private Limited Company

Pallagi út 13.
4042 Debrecen
HUNGARY

TEVA SANTE SA
Rue Bellocier
89100 Sens
France

TEVA UK LIMITED
Brampton Road, Hampden Park
Eastbourne, East Sussex
BN22 9AG
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Stanislav Primožič

PRAC Rapporteur: Margarida Guimaraes

CHMP Peer reviewer(s): N/A

- The application was received by the EMA on 2 July 2014.
- The procedure started on 27 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 25 August 2014
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 September 2014
- During the meeting of 22 to 25 September 2014, 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 26 September 2014
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 November 2014
- During the meeting of 17 to 20 November 2014, the CHMP agreed on the consolidated List of Outstanding Issues to be sent to the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 21 November 2014
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 25 November 2014.
- The Rapporteur circulated the updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 December 2014
- During the meeting of 15 to 18 December 2014, 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 ratiopharm.

2. Scientific discussion

2.1. Introduction

Clopidogrel Ratiopharm 75 mg film-coated tablets is a generic medicinal product containing the active substance clopidogrel as clopidogrel hydrogen sulphate. The reference medicinal product is Plavix 75 mg film-coated tablets, also containing clopidogrel in the form of hydrogen sulphate. Plavix has been centrally authorised on 15 July 1998. Both medicinal products are administered orally. Bioequivalence has been demonstrated to the reference medicinal product.

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 leads 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 Ratiopharm 75 mg film-coated tablet contains clopidogrel hydrogen sulphate. Since this application is a generic application referring to the reference medicinal product Plavix, summary of the clinical data of clopidogrel hydrogen sulphate is available and no new clinical studies regarding pharmacology, pharmacokinetics, efficacy and safety have been conducted with clopidogrel hydrogen sulphate.

The indication proposed for Clopidogrel Ratiopharm is the same as the authorised indication for the reference medicinal product:

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.

Clopidogrel is also indicated in adults for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation in:

• Patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

The application for Clopidogrel ratiopharm is a duplicate application of Clopidogrel Teva (EMEA/H/C/1053), which was approved on 28.7.2009.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablet containing 97.875 mg clopidogrel hydrogen sulphate as active substance corresponding to 75 mg clopidogrel base.

Other ingredients are: (tablet core): lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose (E463), crospovidone (type A), hydrogenated vegetable oil, sodium laurilsulphate, (tablet coating): lactose monohydrate, hypromellose (E464), titanium dioxide (E171), macrogol 4000, iron oxide red (E172), iron oxide yellow (E172) and indigo carmine aluminium lake (E132).

The product is available in Alu/Alu perforated unit dose blisters or Alu/Alu peelable perforated unit dose blisters or HDPE bottles as described in section 6.5 of the SmPC.

2.2.2. Active substance

The chemical name for clopidogrel hydrogen sulphate is methyl(+)-(S)-α-(2-chlorophenyl)--6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulphate (1:1). The active substance is optically active and is presented as the S-enantiomer in the finished product.

Clopidogrel hydrogen sulphate (syn. clopidogrel bisulfate) appears as a white to off-white non-hygroscopic crystalline powder. The clopidogrel hydrogen sulphate selected is sparingly soluble in water at neutral pH, but shows pH dependent solubility (higher solubility in acidic pH). It is freely is soluble in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether.

It exists in several crystalline forms and in an amorphous form. However, this medicinal product contains one pure polymorph form and does not contain any detectable amounts of other forms. The active substance contains one single chiral centre and the S-enantiomer is used in the product. Enantiomeric purity control is included in the active substance specification.

As there is a monograph of Clopidogrel hydrogen sulfate in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Manufacture

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for the additional residual solvents that may be present due to the route of synthesis. The specification includes additional specific tests and acceptance criteria for polymorphic form, particle size, bulk and tapped density. All additional analytical methods have been adequately described and validated according to ICH Q2.

Certificates of analysis of three production scale batches controlled according to the specification were provided. All results comply with the proposed specifications and confirm consistency and uniformity of the product.

Stability

Stability data on five batches (pilot size up to production scale) of active substance from the proposed manufacturer stored in packaging simulating the actual container closure system for 60 months under long term conditions at 25 °C/60 % RH and for 6 months under accelerated conditions at 40 °C/75 % RH according to the ICH guidelines were provided.
Stability data for another 21 production scale batches under long term conditions at 2-8 °C for 36 months and for 9 production scale batches under accelerated conditions at 25 °C/60 % RH for 6 months according to the ICH guidelines were provided.
The stability indicating parameters investigated were: description, identification by enantiomeric purity and polymorphic form, purity and assay. Impurity B (Ph. Eur.) was not tested because this is not a degradation product and therefore it is not expected to increase during storage. The analytical procedures were the same as those for release with the exception of method for assay and all are stability indicating.
A photostability study in compliance with the ICH Guideline Q1B was done. According to the obtained results, active substance is slightly sensitive to light. The proposed packaging is shown suitable for clopidogrel bisulfate storage.
Based on presented stability data, the proposed re-test period and storage conditions are acceptable.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to obtain a stable immediate-release tablet, bioequivalent with the reference medicinal product, Plavix film-coated tablets.

Experimental batches have been prepared in order to select the most suitable excipients and manufacturing method. The choice of excipients has been justified. The excipients used in the formulation comply with the monographs of the current Ph. Eur., except hydrogenated vegetable oil type I and coating mixture Opadry. Hydrogenated vegetable oil type I complies with BP. Opadry II OY-L-34836 pink is specified according to in-house specifications. The ingredients of Opadry, except colorants, also comply with Ph. Eur. The coating colorants meet the relevant requirements for colours for use in foodstuff. Certificates of analysis are provided for all excipients. Based on the results, a formulation containing hydrogenated vegetable oil type I and sodium laurilsulphate as lubricants and crospovidone as disintegrant was selected, manufactured by wet granulation.

Taking into account the solubility of clopidogrel bisulfate form I, particle size distribution is a critical parameter for the performance of the product therefore it is controlled in the active substance specification with limits set according to the biobatch.

The obtained formulations have been compared with Plavix with regards to in-vitro dissolution test results and the impurities in the stability studies. The development and selection of the dissolution test method have been sufficiently described and justified. The discriminatory power of the dissolution method has been demonstrated. Two bioequivalence studies were performed showing bioequivalence between the clinical formulation and the reference product. The formulation used in the bioequivalence studies is the same as the proposed for commercial batches.

Manufacture of the product

The manufacturing process is a standard process and consists of nine steps: premixing, granulation, drying, milling, blending, final mixing, compression, coating and packaging. The manufacturing process

is satisfactorily described and validated. The critical steps in the manufacture of Clopidogrel Ratiopharm (granulation and tableting) are controlled by appropriate in-process controls.

The manufacturing process demonstrated to be reproducible and provides a finished product that complies with the in-process and finished product specifications.

Product specification

The finished product specifications include tests and limits for appearance, identification and assay of the active substance (HPLC), dissolution (Ph. Eur. -HPLC), uniformity of dosage units (Ph. Eur.), impurities (HPLC), microbial contamination (Ph. Eur. - not routinely), water content (Karl Fischer) and identification of colour (Ph. Eur. / HPLC - not routinely).
The analytical methods are described in the Ph. Eur. or are developed in-house. The in-house methods have been satisfactorily described and validated in accordance with the ICH guidelines.

Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety.

Batch analysis results from four pilot batches were submitted (the same batches as for validation of the manufacturing process). The results comply with the proposed specification, indicate that the process is under control and confirm consistency and uniformity of manufacture.

Stability of the product

Stability studies have been performed on 4 pilot scale batches stored for up to 36 months at 25 °C/60 % RH and for six months at 40 °C/75 % RH in accordance with the relevant ICH guidelines. All intended market containers are included in the study. Bulk stability on one batch has been performed. In the stability protocol all stability indicating quality aspects are included: appearance, dissolution, assay, impurities, water and microbiological purity. The analytical methods used are the same as for release testing and are all stability indicating.
A photostability study was performed on one batch as per the relevant ICH guideline. Results showed that the product is not sensitive to light.
In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Adventitious agents
Clopidogrel Ratiopharm contains only one excipient from animal origin. Lactose monohydrate is derived from milk sourced from healthy animals in the same conditions as milk collected for the human consumption. The supplier has provided the required statements on the risk of BSE/TSE.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The active substance is well-known and is described in a Ph. Eur. monograph. The quality of the active substance complies with the Ph. Eur. monograph. The excipients comply with the relevant compendial or adequate in-house specifications. In comparison with the EU reference product, Clopidogrel Ratiopharm contains the same qualitative and quantitative composition in terms of the active substance, however some excipients are different. Both the EU reference product and Clopidogrel Ratiopharm exhibit similar dissolution profiles. The packaging materials are commonly used and well documented. The manufacturing process of the finished product has been adequately described and

controlled with appropriate in process controls. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

Information on development, manufacture and control of the active substance and medicinal product has 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Discussion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of clopidogrel hydrogen sulphate was provided, which was based on up-to-date and adequate scientific literature.

Clopidogrel is a widely used well-known substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. This generic application contains the same salt of the active substance as the reference medicinal product, and the excipients used in the formulation are conventional, well known and broadly used in other medicinal products. Therefore, CHMP agreed that no further studies were required and that a summary of the literature with regard to non-clinical data of clopidogrel hydrogen sulphate was appropriate.

Introduction of the medicinal product onto the market is unlikely to result in any significant increase in the combined sales volumes for all clopidogrel hydrogen sulphate 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 was not considered necessary - the ERA is expected to be similar and not increased.

2.3.2. Conclusion on the non-clinical aspects

The CHMP considered that the non-clinical data provided are adequate to support the clinical use of Clopidogrel ratiopharm.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing clopidogrel hydrogen sulphate. To support the marketing authorisation application, the applicant conducted two bioequivalence studies comparing Clopidogrel Bisulfate 75 mg film-coated tablets with the originator Plavix 75 mg film-coated tablets. Both studies were performed in fasting subjects, one involved measuring the parent drug and another involved measuring the major (inactive) metabolite, clopidogrel carboxylic acid. In addition, one pharmacokinetic study of Plavix 75 mg film-coated tablets was conducted in order to estimate the intra-subject variability of selected pharmacokinetic parameters under fasting conditions.

GCP

The MAH stated that the clinical studies were carried out in accordance with the ICH Good Clinical Practice (GCP) requirements.

Tabular overview of clinical studies

			(Sanofi-Synthelabo Ltd., UK) after a single-dose in healthy male and female subjects under fasting conditions		fasting conditions	included in the pharmacokinetic and statistical analysis.			
BA and BE	2008-1706 Version 1	Module 5 (5.3.1.2)	An estimation of the intra-subject variability of the pharmacokinetic parameters AUCt, AUCinf and Cmax of Plavix® 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) after a single-dose in healthy male and female subjects under fasting conditions	Open-label, single-dose, two-period, single-treatment study	Clopidogrel Bisulfate 75 mg Tablets (Teva Pharmaceutical Industries Ltd.) and Plavix® 75 mg Tablets (Sanofi-Synthelabo Ltd., UK); Film-coated tablets; single-dose; oral under fasting conditions	• Eighteen (18) subjects were dosed in Period 1. • Sixteen (16) subjects were dosed in Period 2, completed the study and are included in the pharmacokinetic and statistical analysis	Healthy subjects	Single dose	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
BA and BE	2007-1362 Version 2	Module 5 (5.3.1.2)	An evaluation of the comparative bioavailability between Clopidogrel Bisulfate 75 mg Tablets (Teva Pharmaceutical Industries Ltd.) and Plavix® 75 mg Tablets (Sanofi-Synthelabo Ltd., UK) after a single dose in healthy male and female subjects under fasting conditions	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study	Clopidogrel Bisulfate 75 mg Tablets (Teva Pharmaceutical Industries Ltd.) and Plavix® 75 mg Tablets (Sanofi-Synthelabo Ltd., UK); Film-coated tablets; single-dose; oral under fasting conditions .	• One hundred (100) subjects were dosed in Period 1. • Ninty-seven (97) subjects completed the study and are included in the analysis.	Healthy subjects	Single dose	Complete; Full
BA and BE	2008-1676 Version 1	Module 5 (5.3.1.2)	An evaluation of the comparative bioavailability between Clopidogrel Bisulfate Tablets (75 mg Clopidogrel) (Teva Pharmaceutical Industries Ltd.) and Plavix® 75 mg FC Tablets	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study	Clopidogrel Bisulfate 75 mg Tablets (Teva Pharmaceutical Industries Ltd.) and Plavix® 75 mg Tablets (Sanofi-Synthelabo Ltd., UK); Film-coated tablets; single-dose; oral under	• Twenty four (24) subjects were dosed in Period 1. • Twenty three (23) subjects were dosed in Period 2 and all 23 completed the study. • Twenty three (23) subjects are	Healthy subjects	Single dose	Complete; Full

Clinical studies

To support the application, the applicant has submitted two bioequivalence studies (studies 2007-1362 and 2008-1676), alongside a pharmacokinetic study of Plavix 75 mg film-coated tablets (study 2008-1706). Study 2008-1676, which determines the bioequivalence based on the data for clopidogrel carboxylic acid, is considered supportive, whereas study 2007-1362 is important for the confirmation of bioequivalence.

2.4.2. Pharmacokinetics

Methods

Study design

Study code 2007-1362: A single-dose, comparative bioavailability study of two formulations of clopidogrel bisulfate 75 mg tablets under fasting conditions

The objective of this study is to evaluate the comparative bioavailability between Clopidogrel Bisulfate 75 mg Tablets (Teva Pharmaceutical Industries Ltd.) and Plavix 75 mg tablets (Sanofi-Synthelabo Ltd., UK) after a single dose in healthy subjects under fasting conditions. This was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study performed on 100 healthy males and females volunteers using a 75 mg single dose. 97 males and females completed the study and data of 97 included in the statistical analysis. Concentrations of clopidogrel were measured from the plasma samples collected over a 36-hour interval after dosing in each period. The study protocol and Informed Consent Form (ICF) were approved by the Ethics Review Board and approved on March 2007. The clinical study was initiated on 14 March 2007 and completed on 22 March 2007.

Study code 2008-1676: A single-dose, comparative biovailability study of two formulations of clopidogrel 75 mg tablets under fasting conditions

The objective of this study is to evaluate the comparative bioavailability between clopidogrel bisulfate tablets (75 mg clopidogrel) (Teva Pharmaceutical Industries Ltd.) and Plavix 75 mg film coated tablets (Sanofi-Synthelabo Ltd., UK) after a single-dose in healthy subjects under fasting conditions. This was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study, designed to evaluate the comparative bioavailability of two formulations of clopidogrel administered to 24 healthy male and female subjects under fasting conditions. Concentrations of clopidogrel carboxylic acid were measured from samples collected over a 36-hour interval after dosing in each period. The study protocol and ICF was submitted to the Ethics Review Board and approved on 24 January 2008. The clinical study was initiated on 29 January 2008 and completed on 6 February 2008.

Study code 2008-1706: A single-dose, pharmacokinetic study of Plavix 75 mg film-coated tablets under fasting conditions

The objective of this study is to estimate the intra-subject variability of the pharmacokinetic parameters AUC_t, AUC_{inf} and C_{max} of Plavix 75 mg Tablets (Sanofi Pharma Bristol-Myers Squibb SNC, France) after a single-dose in healthy subjects under fasting conditions. 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. Concentrations of clopidogrel were measured from the samples collected over a 16-hour interval after dosing in each period. The study protocol and ICF were submitted to the Ethics Review Board and approved on 13 March 2008. The clinical study was initiated on 20 March 2008 and completed on 28 March 2008.

Test and reference products

Study code: 2007-1362

Clopidogrel Bisulfate 75 mg Tablets; Batch No.: K-37665; Teva Pharmaceutical Industries Ltd.

Plavix 75 mg Tablets; Lot No.: BF221; Sanofi-Synthelabo Ltd., UK

Study code: 2008-1676

Clopidogrel Bisulfate Tablets (75 mg Clopidogrel); Batch No.: K-37665; Teva Pharmaceutical Industries Ltd.

Plavix 75 mg FC Tablets; Batch No.: CC314; Sanofi-Synthelabo Ltd., UK

Study code: 2008-1706

Plavix 75 mg Tablets; Lot No.: CE315; Sanofi Pharma Bristol-Myers Squibb SNC, France

Population(s) studied

The selected population in all three clinical trials is in accordance with the N*f*G on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98. Subjects participating in the studies were of different races and met the inclusion criteria and did not fulfil the exclusion criteria described in the study protocol.

Study code: 2007-1362

The population in Study *2007-1362* included non-smoking, male and female volunteers between 18-55 years of age with a BMI between 19 and 30 kg/m^2, who were judged to be healthy based on a medical examination. Ninty-seven (97) subjects completed the study and are included in the analysis.

Drop-outs handling was performed according to the protocol requirements. The protocol deviations were not considered to have impact on the efficacy and safety evaluation.

Study code: 2008-1676

The population in Study *2008-1676* included non-smoking, male and female volunteers between 18-55 years of age with a BMI between 19 and 30 kg/m^2, who were judged to be healthy based on a medical examination. Twenty-three (23) subjects completed the study and are included in the pharmacokinetic and 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.

Study code: 2008-1706

The population in Study *2008-1706* included non-smoking, male and female volunteers between 18-55 years of age (inclusive) with a BMI between 19 and 30 kg/m^2 (inclusive), who were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination. Sixteen (16) subjects were dosed, completed the study and are included in the pharmacokinetic and 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.

Analytical methods

The plasma samples were assayed for clopidogrel and its metabolite using validated LC/MS/MS method. The validation of the LC/MS/MS method has been performed before the new guideline came into force and therefore it was not in line with the current Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009.

As part of the first round responses, the Applicant has provided the scientific justification of the lack of ISR data in accordance with the requirement mentioned in the PKWP Q&A document (EMA/618604/2008 Rev. 9) and thus justified deviations from the above current guideline requirement. CHMP considered that the lack of ISR data was adequately justified.

In conclusion, the applied bioanalytical method was adequately validated and showed acceptable performance during analysis of study samples.

Pharmacokinetic variables

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

Statistical methods

Analysis of variance (ANOVA) was performed on the ln-transformed C_{max}, AUC_{0-t}, AUC_{inf} and to untransformed K_{el} and T_{half} parameters. The significance of the sequence, period and treatment effects and the subject within sequence random effects were tested. Values for the T_{max} parameter were analyzed by a non-parametric approach.

Results

Study code: 2007-1362

Pharmacokinetic parameters of clopidogrel (non-transformed values), N = 97, are presented in the table 2+3 below.

Table 2. Pharmacokinetic parameters for clopidrogrel (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Geometric mean Arithmetic mean	CV%	Geometric mean Arithmetic mean	CV%
$AUC_{(0-t)}$ ($_{ng/ml/h}$)	1.3835 2.1649	122	1.4199 2.3520	127
$AUC_{(0-\infty)}$ (ng/ml/h)	1.5869 2.4083	117	1.6390 2.7134	120
C_{max} ($_{ng/ml}$)	0.9091 1.5739	143	0.9351 1.6516	136
T_{max}* (h)	0.74	45	0.85	116
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max} time for maximum concentration				

*Presented as arithmetic mean (CV%) only.

Table 3. Statistical analysis for clopidogrel (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-t)}$ $AUC_{(0-\infty)}$	97.44 96.82	88.72 to 107.02 87.18 to 107.52	41 40
C_{max}	97.22	87.43 to 108.10	47
* estimated from the Residual Mean Squares			

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_{0-t} and AUC_{inf} 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_{max} should be within 75-133%.

The AUC_{0-t}, $AUC_{0-\infty}$, C_{max} were considered as primary parameters for bioequivalence conclusion with the proposed acceptance range of 80-125% for the AUC and 75-133% for the C_{max} defined in the study protocol. The 90% confidence intervals for AUCt and AUCinf proposed for study 2007-1362 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, widening of the limits for bioequivalence conclusions for Cmax values was not acceptable according to the current CHMP recommendations. Nevertheless, since the Cmax results of the study are within the standard 80-125% limits required by the N*f*G on Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, the proposal for widening the confidence intervals for C_{max} is not of importance. Differences in tmax between test and reference products were not considered to be clinical relevant.

Study code: 2008-1676

Pharmacokinetic parameters of clopidogrel carboxylic acid (non-transformed values), N=23, are presented in the table 4+5 below.

Table 4. Pharmacokinetic parameters for clopidrogrel carboxylic acid (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Geometric mean Arithmetic mean	CV%	Geometric mean Arithmetic mean	CV%
$AUC_{(0-t)}$ ($_{ng/ml/h}$)	9492.2 9786.1	24	9745.2 10034.4	25
$AUC_{(0-\infty)}$ (ng/ml/h)	9850.0 10142.8	24	10081.9 10381.5	25
C_{max} ($_{ng/ml}$)	3453.0 3597.8	28	3589.3 3780.0	28
T_{max}* (h)	0.68	30	0.73	15
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max} time for maximum concentration				

*Presented as arithmetic mean (CV%) only.

Table 5. Statistical analysis for clopidrogrel carboxylic acid (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-t)}$ $AUC_{(0-\infty)}$	97.40 97.70	95.30 to 99.55 95.14 to 100.33	4 5
C_{max}	96.20	88.11 to 105.04	17
* estimated from the Residual Mean Squares			

The 90% confidence interval values for the ln-transformed pharmacokinetic parameters of $C_{max,}$ AUC_t and AUC_{inf} are within the acceptance range of 80-125% as defined in the study protocol. Low intra-subject variability for all pharmacokinetics parameters has been shown. No pre-dose levels of clopidogrel carboxylic acid are observed before period 2 drug administration and no subject reached C_{max} at the first sample time, indicating that the sampling period is adequate. T_{max} is not significantly different between test and reference products. Calculated intra-subject variability was reasonably low for clopidogrel carboxylic acid.

Study code: 2008-1706

Pharmacokinetic parameters of clopidogrel (non-transformed values), N=16 are presented in table 6+7 below.

Table 6. Pharmacokinetic parameters for clopidrogrel (non-transformed values)

Pharmacokinetic parameter	Period 1		Period 2	
	Geometric mean Arithmetic mean	CV%	Geometric mean Arithmetic mean	CV%
$AUC_{(0-t)}$ ($_{ng/ml/h}$)	0.9429 1.9818	168	0.9397 1.8782	138
$AUC_{(0-\infty)}$ (ng/ml/h)	1.0809 2.4966	154	1.2825 2.5981	117
C_{max} ($_{ng/ml}$)	0.5527 1.4782	188	0.6710 1.4349	150
T_{max}* (h)	0.71	22	0.79	60

Pharmacokinetic	Period 1	Period 2
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours	
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours	
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity	
C_{max}	maximum plasma concentration	
T_{max}	time for maximum concentration	

*Presented as arithmetic mean (CV%) only.

Table 7. Statistical analysis for clopidrogrel (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-t)}$ $AUC_{(0-\infty)}$	100.33 84.28	78.99 to 127.45 63.80 to 111.33	40 33
C_{max}	82.36	67.32 to 100.77	33
* estimated from the Residual Mean Squares			

Pharmacokinetic study 2008-1706 was conducted to establish whether Plavix 75 mg film-coated tablets is a medicinal product with a high pharmacokinetic intra-individual variability. Based on the results of this single study, Plavix showed an intra-subject variability of >30%. However, the CHMP considered that although these data could indicate high within-subject variability, it has not been definitely established that clopidogrel is a "highly variable" drug and the results do not justify such assumption. It is also unlikely that the power of study 2008-1706 could be considered acceptable to justify this conclusion, since only a limited number of subjects participated in this trial.

Safety data

Study code: 2007-1362

No serious adverse events (SAEs) occurred in study 2007-1362. There were 130 adverse events (AEs) involving 46 subjects in the study. The most commonly reported AEs associated with clopidogrel were blood GGT, AST, ALT increased, loose stool, light-headedness, abdominal pain, elevated urea in blood, increased creatinine, headache and other. The AEs were believed not to have a significant impact on the safety of the subjects or on the integrity of the study results. Tolerability of the test product was found to be acceptable.

Three subjects withdrew; two subjects withdrew due to personal reasons and one subject was dismissed from the study after period 2 dosing due to missed blood draws. There were post-dose blood sampling deviations and one subject refused to provide blood samples for post-study haematology and serum chemistry tests. The protocol deviations were not considered to have an impact on the efficacy and safety.

Study code: 2008-1676

No serious adverse events (SAEs) occurred during the study. There were 24 adverse events (AEs) involving 12 subjects in the study. Amongst the adverse events reported in relation to the drug was dizziness, somnolence or increased levels of creatinine. The AEs were believed not to have a significant impact on the safety of the subjects or on the integrity of the study results.

One subject was dismissed from the trial prior to check-in for period 2 due to an adverse event rectal bleeding. There were some post-dose blood sampling deviations greater than or equal to 1 minute deviations from the scheduled sampling time. These were accounted for during the pharmacokinetic analysis. No other protocol deviations were noted in this study and those that occurred were not considered to have impact on the efficacy and safety evaluation.

Study code: 2008-1706

No SAEs occurred during the study 2008-1706. The AEs related to the drug such as headache, vomit, nausea, dizziness, abdominal pain, fatigue and blurred vision, were reported. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Two subjects were withdrawn due to adverse events (headache, nausea, emesis, sore throat, cough, dizziness and feeling hot). There were some post-dose blood sampling deviations greater than or equal to 1 minute and deviations from the scheduled sampling time. The handling of drop outs was performed according to the protocol requirements. Protocol deviations were not considered to have impact on the efficacy and safety evaluation.

Conclusions

Based on the presented bioequivalence studies Clopidogrel ratiopharm is considered bioequivalent with Plavix.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

The clopidogrel containing medicinal products from Teva group have been marketed in EEA and non-EEA. Therefore post-marketing data for those products are available for the period 31.1.2007-17.11.2013. The assessment of safety data was prepared within PSUSA procedure No. PSUSA/00000820/201311.

2.4.5. Discussion on clinical aspects

Application for Clopidogrel ratiopharm is a duplicate application of Clopidogrel Teva 75mg film-coated tablets (EMEA/H/C/1053), which was centrally authorised on 28 July, 2009.

Overall discussion on clinical aspects discussed initially in 2009 and currently is summarised below.

Two clinical bioequivalence trials were provided for Clopidogrel ratiopharm (clopidogrel hydrogen sulphate) and also one pharmacokinetic study with the reference product. At the time of approval of the reference product Plavix (clopidogrel hydrogen sulphate), 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 major non-active metabolite. In the meantime, a reliable bio-analytical method for determination of clopidogrel in plasma and urine has been developed. Since the pharmacokinetic profile of the active metabolite is still not well established, the CHMP accepted in 2009 the proof of bioequivalence based on the clopidogrel parent compound data.

Thus, study 2008-1676, which determines the bioequivalence based on the data for clopidogrel carboxylic acid, is considered supportive, whereas study 2007-1362 is important for the confirmation of bioequivalence.

The published literature indicated 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 several fold 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. 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 (EMEA/CHMP/EWP/40326/2006) document as this situation would be more sensitive to differences in pharmacokinetics. In addition the dissolution studies using clopidogrel hydrogen sulphate conducted at three different pH values (1.2, 4.5 and 6.8) and mimicking the conditions of a fed state did not show any major differences between the originator and the generic 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 huge over-estimation of clopidogrel plasma levels and would bias the outcome of the bioequivalence study. Demonstration of the lack of back-conversion of clopidogrel carboxylic acid metabolite to the parent drug under all conditions for sample handling and storage was requested by the CHMP. After review of additional experimental data the CHMP considered the issue resolved.

In addition, the validity of the bioanalytical method (lack of ISR) in the Bioequivalence study 2007-1362. The Applicant has adequately justified the lack of incurred sample reanalysis (ISR) therefore CHMP considers this issue to be solved.

The bioequivalence study 2007-1362 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, as required by the above mentioned guideline.

Study 2008-1706 aimed to demonstrate the proposed high variability of Plavix, however, the CHMP did not consider this stand alone clinical trial sufficient to establish Plavix as a drug with a highly variable pharmacokinetics due to its inadequate design and limited number of participants. Therefore, the proposed widening of the 90% confidence interval for clopidogrel C_{max} to 75%-133% on the basis that clopidogrel belongs to a group of drugs with high variability 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.

2.4.6. Conclusions on clinical aspects

The application contains adequate review of clinical data published in the literature and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, CHMP considers the Summary acceptable.

2.6. Risk management plan

The Applicant has submitted updated Risk Management Plan, version 3.1, dated 14 October 2014 in the format of the RMP in the EU for generics, which is acceptable.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.1 is acceptable. The applicant implemented the changes in the RMP as requested in the PRAC endorsed PRAC Rapporteur assessment report of version 3.0 dated 11 September 2014.

The CHMP endorsed the Risk Management Plan version 3.1 with the following content:

Safety concerns

Summary table of safety concerns

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

Pharmacovigilance plan & Risk minimisation measures

The applicant proposed routine pharmacovigilance and risk minimisation activities for each safety concern. There are no additional activities planned.

2.7. PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product.

2.8. Product information

2.8.1. User consultation

User testing for Clopidogrel ratiopharm 75 mg film-coated tablets was conducted with adequate participants. The company that performed the user testing conducted the pilot phase with 2 participants before the first round of user testing.

The questions prepared covered the main safety issues of PIL adequately. The methodology of user testing was suitable and results well documented. After two rounds of user testing the criteria for the satisfactory test outcome (90% of participants were able to find the requested information in PIL and 90% of them understood it) were met. No further changes of the tested PIL were necessary. Based on the results in both rounds, no further testing is considered necessary.

Therefore, the results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The PIL submitted in the registration procedure EU/H/C/4006 is compliant with the PIL used in user testing and is identical in content.

3. Benefit-risk balance

This application concerns a generic version of clopidogrel hydrogen sulphate film-coated tablets. The reference product, Plavix 75 mg film-coated tablets, is indicated for: prevention of atherothrombotic events in:

• Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

• Adult patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).

- ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

and

prevention of atherothrombotic and thromboembolic events in atrial fibrillation in:

• Adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

Bioequivalence of the two formulations (Clopidogrel ratiopharm and the reference product Plavix) was demonstrated.

The application contained adequate quality, non-clinical and clinical data, and bioequivalence was shown. Taking into account the Applicant's responses to the questions throughout the procedure, CHMP considers that the benefit/risk ratio comparable to the reference product can therefore be concluded.

Also, 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.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP consider by consensus that the benefit-risk balance of Clopidogrel ratiopharm in the approved indications of:

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.

and

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation in

• Patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke

is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.