ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT IN THE MEMBER STATES

Member State EU/EEA	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration
Czech Republic	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Denmark	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Finland	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Germany	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Latvia	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Lithuania	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Norway	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Slovak Republic	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use
Sweden	Orion Corporation Orionintie 1, FI-02200 Espoo Finland	Clopidogrel Orion	75 mg	Film-coated tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CLOPIDOGREL ORION

Clopidogrel is a non-competitive inhibitor of adenosine diphosphate (ADP) at the platelet receptors. 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 indicated for the prevention of atherothrombotic events in patients suffering from myocardial infarction or acute coronary syndrome. The product is formulated as immediate release tablets containing 75 mg clopidogrel.

The legal basis under which the application was submitted is Art 10(1) in combination with Art. 28(3) of Directive 2001/83/EC, as amended.

The reference medicinal product for this generic application is Plavix (Clopidogrel Hydrogen sulphate) 75 mg film-coated tablets. In contrast to the reference product that contains the hydrogen sulphate salt, the generic product contains a clopidogrel base. As the clopidogrel base corresponds to an unstable, viscous mass, the drug substance is stabilized by means of a premix, which contains the antioxidant butylated hydroxy anisol (BHA).

This was not considered to be acceptable by the objecting Concerned Member State (CMS) as there are stable salts available, and the use of the clopidogrel base was considered to result in an unnecessary exposure of patients to an antioxidant. The issue was referred to the CMD(h) and an assessment was carried out by the Reference Member State (RMS). Because no agreement was reached at Day 60, the procedure was referred to the CHMP. The CHMP assessed the dossier and the available data, including the issues raised by the objecting CMS.

- Quality issues

The Applicant defended the objection that not all possible salts had been considered. It was argued that at that time, the potential to develop a salt with suitable pharmaceutical and pharmacological properties, and free from any FTO (freedom-to-operate) issues later, was thoroughly literature researched. Taking into consideration the literature survey, the taurocholate, hydrochloride, hydrobromide and hydrogen sulphate salts and free base of clopidogrel were considered.

Based on the information presented, taurocholate, hydrochloride, hydrobromide and hydrogen sulphate salts of clopidogrel were found to be unsuitable for product development for various reasons. Although the clopidogrel free base posed the challenges of converting an unstable, gummy and sticky nature into a granular, free flowing and stable material for use in formulations, the Applicant chose the clopidogrel free base as the suitable candidate for product development.

In order to circumvene the challenges of using the clopidogrel base, it was essential to convert it into a granular and free flowable material. Hence a premix development using a suitable vehicle was considered. The premix approach was thought to help in the flow property of clopidogrel base.

Clopidogrel is known to hydrolyse and to form a hydrolytic impurity i.e an acetic acid impurity, which is a major degradant. The product developed with clopidogrel premix was found to be non-hygroscopic. The acetic acid impurity (a major degradant) was found to be controlled in the Applicant’s clopidogrel Tablets 75 mg as compared to Plavix 75 mg (Clopidogrel Bisulphate Tablet 75 mg).

From the data provided the Applicant claimed that clopidogrel tablets 75 mg are stable when compared to Plavix 75 mg (Clopidogrel Bisulphate Tablets 75 mg).

In addition, the CHMP was also concerned that it had not been demonstrated that the proposed production and quality control methods could guarantee that a major deficiency in the quality of the product would not

occur. Therefore justification that the overall control strategy ensured suitable and reproducible quality of the product with regard to the handling of the viscous mass of clopidogrel base was requested from the Applicant and justification also for the absence of specifications for the clopidogrel base.

The Applicant explained that to make it feasible for better handling, it was decided to add the excipient BHA, which in turn resulted in a stable clopidogrel premix. Since the nature of the base made it unsuitable to incorporate appropriate in-process quality checks for the clopidogrel base, the Applicant has attempted to control the quality of the base produced by ensuring the quality of the intermediate.

The manufacturing process has been successfully validated with three batches. Batch analysis results have demonstrated consistent quality. The overall control strategy to ensure suitable and reproducible quality of the product has been justified with regard to the handling of the viscous mass of the clopidogrel base, and the proposed specifications for the clopidogrel base are considered to be acceptable by the CHMP.

The Applicant attended the CHMP meeting for an oral explanation on 17 February 2010 to present their position with regard to the choice of clopidogrel base as the active substance compared to the more stable clopidogrel salts, and also to discuss the safety of the long-term use of BHA.

The CHMP noted that the primary purpose for the addition of BHA was to prevent the initiation of free radicals, by blocking the oxidative pathway, and was assured by the Applicant that the lowest level possible had been used. In conclusion, the CHMP agreed that although the choice of the clopidogrel base was not considered to be optimal, the use of BHA and the production process did not pose a potentially serious risk to public health.

- Clinical issues

The use of the unstable clopidogrel base as active substance necessitated the use of the antioxidant butylated hydroxyl anisol (BHA) for stabilisation. It was argued by the objecting CHMP members that according to the Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (EMEA/CHMP/QWP/396951/2006) and the Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products (CPMP/CVMP/QWP/115/95), the use of antioxidants should be avoided whenever possible. Furthermore the objecting CHMP members pointed out that in both guidelines, it is also stated that antioxidants should not be used to disguise poorly formulated products.

The Applicant addressed the long-term safety of BHA at the oral explanation before the CHMP on 17 February 2010, by making reference to the Acceptable Daily Intake (ADI), an estimate of the amount of BHA that can be ingested on a daily basis over a lifetime without appreciable risk to health. The Applicant explained that the amount of BHA from clopidogrel tablets was no more than 0.75% of its ADI, which was argued to be a negligible.

Furthermore BHA is an approved and widely used food additive (E 320) in the European Union. Therefore the chosen antioxidant BHA and the concentration in which it is used, was considered to be acceptable by the CHMP, from a safety point of view.

In the bioequivalence study, a total of 19 adverse events were reported by 13 subjects. Three out of the nineteen adverse events did not require any medical intervention. Out of 19 adverse events observed, 14 were for the reference product and 5 were for the test product. When clopidogrel bisulfate (as in Reference product) and clopidogrel base (as in Test product) were administered as a single dose to healthy volunteers in this study, the drug products were well tolerated with no serious adverse events for either, and no relevant difference in the safety profiles of the test and reference formulation was observed with regard to the number and pattern of adverse events.

The Applicant also claimed that the test product when compared with the reference product Plavix, met the bioequivalence criteria with respect to the rate and extent of absorption of clopidogrel.

Overall, it is claimed by the Applicant that their clopidogrel tablets 75 mg has adequate quality and benefit/risk ratio and is comparable to the reference product. It is also argued that in view of the above, the selection of the clopidogrel base and the development of the clopidogrel premix had been justified for its use in generic formulation. The chosen clopidogrel base necessitated the use of an antioxidant which was not considered to be optimal. However in view of the fact that no major concerns were found in relation to quality of the product and that the use of antioxidant did not pose a safety concern, the CHMP accepted the choice of the clopidogrel base.

The CHMP agreed that the Applicant's choice of the clopidogrel base and consequently the use of BHA had been sufficiently explained. The drug substance and the drug product manufacturer have been shown to be capable of producing a, stable product essentially similar in efficacy and safety to the reference product. The Clopidogrel Orion 75 mg Film coated Tablets:

- are stable in comparison to clopidogrel bisulphate, which is sensitive to hydrolytic degradation.

- are bioequivalent to the reference medicinal product clopidogrel bisulphate

- in the view of the CHMP, do not differ with regard to safety relevant properties. BHA is present in amounts less than the ADI, which is generally deduced from the No Effect Level of the substance; therefore a biological action or effect on the patients is not expected.

GROUNDS FOR POSITIVE OPINION

Whereas

- the Applicant's choice of the clopidogrel base and consequently the use of BHA has been sufficiently explained

- the overall control strategy to ensure suitable and reproducible quality of the product has been justified with regard to the handling of the viscous mass of the clopidogrel base

- the Applicant's Clopidogrel Base Tablets 75 mg has adequate quality and benefit/risk ratio and is comparable to the reference product

the CHMP has recommended the granting of the Marketing Authorisation for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of this Opinion.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.