ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Scientific conclusions

Overall summary of the scientific evaluation of Norvasc and associated names (see Annex I)

Norvasc (amlodipine) is a calcium ion antagonist of the dihydropyridine group. Amlodipine reduces myocardial ischemia through the dilation of the main coronary arteries, improving oxygen delivery to the heart, and through the reduction of peripheral resistance (afterload), decreasing myocardial oxygen consumption.

Due to the divergent national decisions taken by Member States concerning the authorization of the above-mentioned product, Pfizer Limited (on behalf of the national marketing authorisation holders) notified the EMA of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SPCs for the above-mentioned product and thus to harmonise its SPCs across the EU.

- **Quality issues**

The MAH took the opportunity to harmonise the Quality dossier for Norvasc and associated names as part of the referral procedure.

The harmonised dossier was provided for the active substance (amlodipine besylate) and for products containing this substance: Norvasc 5 mg and 10 mg tablets, Norvasc 5 mg and 10 mg capsules.

Harmonisation of the dossier for the active substance was achieved by introduction of a Certificate of Suitability with requirements of European Pharmacopoeia (CEP). The CEP certified amlodipine besylate will be the only source of the active substance that will be used for manufacturing of tablets and capsules.

Information on development, manufacture and control of tablets and capsules 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 these products should have a satisfactory and uniform performance.

Both for tablets and capsules, the shelf-life is supported by relevant stability data. The storage precaution “Do not store above 30°C” is included in the product information for capsules. The storage precaution “Do not store above 25°C” is included in the product information for tablets.

- **Efficacy and safety issues**

Section 4.1 – Therapeutic Indications

The primary indication of angina and hypertension is approved in all EU member states. The specific indication for vasospastic (Prinzmetal’s) angina is approved in all EU member states except Denmark, Iceland, Norway and Sweden. The data supporting the proposed indications of hypertension, chronic stable angina pectoris and vasospastic (Prinzmetal’s) angina were considered to be acceptable by the CHMP and the following wording proposed by the MAH was agreed:

‘Hypertension

Chronic stable angina pectoris

Vasospastic (Prinzmetal’s) angina’

Section 4.2 - Posology and method of administration

Dosing instructions (including maximum dose) are harmonised in all EU countries. All countries recommend an adult starting dose of 5 mg which may be increased to a maximum of 10 mg. The CHMP was of the view that the text proposed by the MAH is supported by the data submitted with the initial application.

Most but not all countries have dosing recommendations for use in combination with antihypertensive medicinal products. Only Austria, Cyprus and Greece have a statement on use in combination with antianginal drugs. The CHMP agreed that combination therapy using two and recently even three antihypertensive medicinal products is common practice, as it is recommended by hypertension treatment guidelines internationally. Combination therapy with other antianginal medicinal products was also considered to be acceptable and is reflected adequately in this section of the SmPC.

Currently the MAH does not have a dosage form approved in the EU that delivers 2.5 mg amlodipine for use in the paediatric population. Since the breakability of the scored 5mg tablet had not been approved or submitted anywhere in the EU at the start of this Art 30 referral procedure, it was therefore considered to be outside the scope of this procedure.

Administration in elderly and patients with renal impairment is already aligned in the vast majority of EU member states. Most countries recommend normal adult doses in the elderly without qualification. Normal adult doses are also recommended for the elderly and also in patients with renal impairment.

Half-life was longer in patients with hepatic impairment than in healthy patients. Additionally, the area under the curve (AUC) was higher in patients with hepatic impairment than in healthy patients. Dosing recommendations have not been established and thus the MAH considered it appropriate to recommend caution when administering amlodipine to patients with hepatic impairment.

Section 4.3 - Contraindications

The Contraindications Sections is in line with the Core Safety Profile (CSP) that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001- completed 18 May 2009. Therefore the CHMP agreed that Section 4.3 can be accepted with the wording proposed by the MAH.

The CHMP agreed with the following wording proposed by the MAH:

'Amlodipine is contraindicated in patients with:

- *hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients.*
- *severe hypotension.*
- *shock (including cardiogenic shock).*
- *obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).*
- *haemodynamically unstable heart failure after acute myocardial infarction.'*

Section 4.4 - Special warnings and precautions for use

The statement on the use of amlodipine in children in the proposed harmonised SmPC, is based on the outcome of the Article 45 Paediatric Procedure, which is included in section 4.2, where dosing recommendations for children aged 6 to 17 years are provided.

The CHMP noted that section 4.4 is in line with the CSP that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001 and completed 18 May 2009. However more detailed information on dosing recommending caution in patients with hepatic impairment based on the fact that very limited data are available was agreed by the CHMP and included in this section.

In addition a cautionary statement on patients with heart failure, as well as a general statement that calcium channel blockers may increase the risk of future cardiovascular events and mortality in patients with congestive heart failure was also included.

Section 4.5- Interaction with other medicinal products and other forms of interaction

The CHMP was of the view that the potential interaction of amlodipine with antihypertensive agents is adequately covered in the SmPC proposed by the MAH. However the CHMP was of the view that the published data provided by the MAH are not sufficient to support the claim for lack of interactions with non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs, since they are not extracted from specifically designed Pharmacokinetic/interaction studies. Therefore CHMP was of the view that this information should be excluded from Section 4.5.

Section 4.6 - Pregnancy and lactation

All countries have approved or are implementing the EU Workshare CSP 4.6 text adopted in the proposed SmPC.

However the CHMP recommended some amendments to the sections on pregnancy and fertility. As there have been a number of publications concerning sperm anomalies in human and animal studies, the MAH agreed to update the section on fertility stating that although clinical data are insufficient regarding the potential effect of amlodipine on fertility, adverse effects on male fertility have been found in one rat study.

A brief statement on reproductive toxicity in animal studies was also added by the MAH under the section pregnancy (and cross references to section 5.3) in response to the CHMP's recommendation.

Section 4.7 - Effects on ability to drive and use machines

All countries except Germany and Austria have approved or are implementing the EU Workshare CSP 4.7 adopted text. The text included in the German and Austrian product information texts recommends caution especially at the beginning of treatment, during adjustment of dosage, switching of therapy and in case of concomitant alcohol consumption. However the MAH believes the CSP text adopted in the proposed harmonised SmPC adequately covers this point, and is supported by the CHMP.

Section 4.8 - Undesirable effects

The CHMP accepted the wording proposed by the MAH for Section 4.8, which is in line with the Core Safety Profile that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001 on 18 May 2009. In addition the CHMP recommended that extrapyramidal syndrome (EPS) is also included, since EPS had already been discussed in the PSUR WS procedure that was concluded on May 2009, and further review is expected to take place during the assessment of the second PSUR WS scheduled for May 2011. The MAH accepted the inclusion of EPS as recommended by the CHMP.

Section 4.9 – Overdose

All countries follow the exact EU Workshare CSP section 4.9 text or similar text. The CHMP accepted the wording proposed by the MAH for section 4.9, which is in line with the CSP that was accepted during the PSUR Worksharing procedure DK/H/PSUR/0007/001 and completed 18 May 2009.

Section 5.1 - Pharmacodynamic properties

The information on the pharmacology and the mode of action is broadly consistent across the EU Member States.

Regarding the effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD), the results of the CAMELOT (Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis) study were considered to be acceptable, and a revised table with

data from the enalapril treatment arm as well as the full set of components of the composite outcome as suggested by the CHMP was included by the MAH in this section.

The MAH agreed to delete the summary based on the PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial) study results, since the CHMP was of the view that this study had been over-interpreted and should therefore not be included.

Regarding the use of amlodipine in patients with heart failure, the studies PRAISE (Prospective Randomized Amlodipine Survival Evaluation) and PRAISE-2 are described. These placebo-controlled studies showed that there was no difference between amlodipine and placebo in all-cause mortality. However there appeared to be an increased incidence of pulmonary oedema as an adverse event in this patient population.

ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which was a large, randomized controlled trial that provided extensive mortality and morbidity data is also described in this section. ALLHAT which compared newer drug therapies: amlodipine or lisinopril (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone in mild to moderate hypertension, demonstrated that amlodipine had effects comparable to those of diuretics (an established standard), on cardiovascular events across all patient subgroups.

The proposed harmonised text regarding use in children has been agreed in the Article 45 Paediatric Procedure NL/W/0002/pdWS/001 that was completed on 21 October 2009, and was considered to be acceptable by the CHMP.

Section 5.2 - Pharmacokinetic properties

The basic texts on pharmacokinetic properties within the Norvasc EU national SmPCs are supported by the data submitted with the marketing authorisation application, and are similar or identical to the text in the proposed harmonised SmPC.

However the data provided from an open study to assess the safety and pharmacokinetic profile of oral amlodipine in patients with stable chronic hepatic insufficiency (n=12) compared with a group of convalescing subjects without hepatic impairment (n=8) were considered to be of poor quality, and the CHMP was of the view that a summary of this study should not be included in this section of the SmPC. The MAH agreed to exclude the summary of this study, stating only that very limited clinical data are available and that patients with hepatic impairment have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC.

The pharmacokinetics of amlodipine has not been studied in patients with severe hepatic impairment.

The proposed harmonised SmPC 5.2 text regarding use in children is the agreed text from the Article 45 Paediatric Procedure. The use in the elderly text is also similar across the EU national SmPCs for amlodipine, according to CSP.

Section 5.3 - Preclinical safety data

The proposed harmonised SmPC wording for section 5.3, which included brief summaries of reproductive toxicology, carcinogenesis and mutagenesis was considered to be acceptable by the CHMP.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet

- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Norvasc and associated names (see Annex I).