Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for amlodipine, the scientific conclusions are as follows:

Based on review of literature data, the PRAC considered that a causal relationship between the use of amlodipine and the occurrence of Toxic epidermal necrolysis (TEN), could not be excluded and therefore requests an update of the product information to insert this adverse drug reaction with the frequency not known. Additionally, section 4.5 was updated to reflect the information on the concomitant use of CYP3A4 inducers, such as Rifampicin, with additional instructions for patients. Moreover, section 4.6 will be updated to reflect the presence of amlodipine in breast milk of lactating women. The Package Leaflet was updated accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for amlodipine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing amlodipine is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing amlodipine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.5

CYP3A4 inhibitors

(…)

CYP3A4 inducers

~~There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers~~.

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

- Section 4.6

Amlodipine is excreted in human milk . The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. ~~It is not known whether amlodipine is excreted in breast milk.~~ A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and Subcutaneous Tissue Disorders with a frequency Unknown:

Toxic Epidermal Necrolysis

Package Leaflet

2. What you need to know before you take <Product name>

Other medicines and <Product name>

(…)

<Product name> may affect or be affected by other medicines, such as:

- **rifampicin, erythromycin, clarithromycin (antibiotics)**

Pregnancy and breast-feeding

(…)

Breast-feeding

~~It is not known whether a~~**Amlodipine** ~~is~~ **has been shown to** pass~~ed~~ into breast milk **in small amounts**. If you are breastfeeding or about to start breast-feeding you must tell your doctor before taking [product name].

4. Possible side effects

Visit your doctor immediately if you experience any of the following side effects after taking this medicine.

• Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome**, toxic epidermal necrolysis**) or other allergic reactions

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	25 November 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	24 January 2018