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 nicardipine, the scientific conclusions are as follows:

Nicardipine is a Ca(2+) channel blocker (CCB) that inhibits the CYP3A4. Tacrolimus is a calcineurin inhibitor, used as an immunosuppressive drug to prevent organ rejection, primarily metabolised by cytochrome P450 3A4.

Increasing concentrations of tacrolimus is due to the inhibition of CYP3A4 by nicardipine with the consequent inhibition of tacrolimus metabolism. Tacrolimus is also metabolized by CYP3A5 which is a secondary pathway that becomes important when CYP3A4 is inhibited. CYP3A5 is not genetically expressed in all subjects. In patients genetically lacking the alternative pathway for tacrolimus metabolism, CYP3A5, nicardipine could lead to tacrolimus overexposure and to toxic concentrations.

Based on this pharmacokinetic interaction, it is cautiously recommendable the therapeutic drug monitoring of immunosuppressant tacrolimus (sirolimus and cyclosporine) in presence of the concomitant administration of nicardipine to maintain safe and effective immunosuppressive treatment with the appropriate adjustment of the dosage.

The product information of most nicardipine medicinal products does not mention the interaction between tacrolimus and nicardipine consistently. However, in view of the data presented in the reviewed PSURs, in particular the literature publications on the interaction between nicardipine and tacrolimus, the PRAC considered that changes to the product information of medicinal products containing nicardipine were warranted. The section 4.5 of summary of product characteristics of nicardipine medicinal products should be amended by adding the active substance "tacrolimus" to the already existing wording regarding cyclosporine as well as the advice to monitor tacrolimus plasma level. Moreover, sirolimus should also be added in the warning of the interaction between nicardipine and CYP3A4 inhibitors such as cyclosporin and tacrolimus.

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 nicardipine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing nicardipine 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 {active substance(s) as EURD list entry} are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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**

A warning should be revised as follows:

[...]

Cyclosporine, tacrolimus and sirolimus :
Concomitant administration of nicardipine and cyclosporine, tacrolimus or sirolimus results in elevated plasma cyclosporine, tacrolimus or sirolimus levels. Cyclosporine, tacrolimus or sirolimus level should be monitored and dosage of immunosuppressant and/or nicardipine should be reduced, if required.

[...]

Package Leaflet

2. What you need to know before you use [invented name of product]

Other medicines and [invented name of product]

Tell your doctor, pharmacist or nurse if you are using, have recently used or might use any other medicine.

[...]

Especially tell your doctor if you are using other medicines used to control the body's immune system such as cyclosporine, tacrolimus or sirolimus.

[...]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 May 2017