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 ezetimibe / rosuvastatin, the scientific conclusions are as follows:

- **DRESS**

In view of available data on Drug reaction with eosinophilia and systemic symptoms (DRESS) from the literature including in five cases a close temporal relationship, a positive de-challenge and one case of positive re-challenge and ”definite” DRESS (according to PRAC Serious Cutaneous Adverse Reactions (SCARs) guideline) in two cases, the PRAC considers a causal relationship between rosuvastatin and DRESS is established. The PRAC concluded that the product information of products containing rosuvastatin should be amended accordingly.

- **Interaction between ticagrelor and rosuvastatin**

In view of available data on rhabdomyolysis as a result of the interaction between ticagrelor and rosuvastatin from the literature including in all cases a positive dechallene and in view of a plausible mechanism of action, the PRAC considers that the interaction between rosuvastatin and ticagrelor resulting in rhabdomyolysis is established. The PRAC concluded that the product information of products containing rosuvastatin should be amended 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 ezetimibe / rosuvastatin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing ezetimibe / rosuvastatin 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 ezetimibe / rosuvastatin 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~~)

DRESS:

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin. At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appears, <medicine> should be discontinued immediately and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of <medicine>, treatment with <medicine> must not be restarted in this patient at any time.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency not known:

Frequency not known: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Package leaflet

- Section 2 - What you need to know before you use <medicine>

DO NOT TAKE <medicine> - OR - TELL YOUR DOCTOR BEFORE TAKING <medicine>:

- **If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking <medicine> or other <related medicines>.**

Warnings and precautions - Take special care with <medicine>:

Serious skin reactions including Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with <medicine> treatment. Stop using <medicine> and seek medical attention immediately if you notice any of the symptoms described in section 4.

- Section 4 - Possible side effects

Stop using <medicine> and seek medical attention immediately if you notice any of the following symptoms:

- **reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).**

- **Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).**

[…]

Side effects of unknown frequency may include:
[…] ~~Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals)~~

Interaction between ticagrelor and rosuvastatin:

Summary of Product Characteristics

- Section 4.5

The interactions/s should be added as follows:

Ticagrelor: Ticagrelor can cause renal insufficiency and may affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. In some cases, co-administered ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis. Renal function and CPK control is recommended while using ticagrelor and rosuvastatin concomitantly.

Package leaflet

- Section 2 - What you need to know before you take <medicine>

Other medicines and rosuvastatin

Tell your doctor if you are taking any of the following:

- Blood thinners e.g. warfarin, acenocoumarol or fluindione (their blood thinning effect and the risk of bleeding may be increased while taken together with this medicine), **ticagrelor** or clopidogrel.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 May 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	8 July 2021