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 atorvastatin, the scientific conclusions are as follows:

In view of available data on myopathy and rhabdomyolysis following concomitant use of atorvastatin and daptomycin, on lichenoid drug reaction and on vasculitis from literature, spontaneous cases, including some cases with a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between myopathy and rhabdomyolysis following concomitant use of atorvastatin and daptomycin, between atorvastatin and lichenoid drug reaction and between atorvastatin and vasculitis is at least a reasonable possibility. The PRAC concluded that the product information of medicinal products containing atorvastatin should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

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

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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 4.4

A warning should be added as follows:

Concomitant treatment with other medicinal products

[…]

The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors (e.g. atorvastatin) and daptomycin (see section 4.5). Consideration should be given to temporarily suspend <product name> in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CK levels should be measured 2-3 times per week and patients should be closely monitored for any signs or symptoms that might represent myopathy.

- Section 4.5

An interaction should be added as follows:

[…] Effects of other medicinal products on <product name>

[…]

Colchicine: Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Daptomycin: Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. atorvastatin) co-administered with daptomycin. If co-administration cannot be avoided, appropriate clinical monitoring is recommended (see section 4.4).

[...]

- Section 4.8

The following adverse reaction should be added under the SOC **'Vascular disorders'** with a frequency 'rare':

Vasculitis

The following adverse reaction should be added under the SOC 'Skin and subcutaneous tissue disorders' with a frequency 'rare':

Lichenoid drug reaction

Package Leaflet

- Section 2

An interaction should be added as follows:

[...] What you need to know before you take <product name>

Other medicines and <product name>

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. There are some medicines that may change the effect of Atorvastatin or their effect may be changed by Atorvastatin. This type of interaction could make one or both of the medicines less effective.
Alternatively it could increase the risk or severity of side-effects, including the important muscle wasting condition known as rhabdomyolysis described in section 4:

[…]

- **daptomycin (a medicine used to treat complicated skin and skin structure infections and bacteria present in the blood).**

- Section 4

The following adverse reactions should be added with a frequency 'rare':

[...]

Other possible side effects with <product name>

Rare: may affect up to 1 in 1,000 people

[…]

- **rash that may occur on the skin or sores in the mouth (lichenoid drug reaction)**
- **purple skin lesions (signs of blood vessel inflammation, vasculitis)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 August 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 October 2024