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:

Based on updated information from interaction studies of atorvastatin with the antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, which showed increases in atorvastatin plasma levels with these co-administrations, PRAC concluded that relevant contraindications and warnings as regards these medicines are necessary in order to minimise the risk of dose-related adverse reactions such as myopathy. The Package Leaflet is 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 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 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 atorvastatin are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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

4.2 Posology and method of administration

Posology

[…]

Co-administration with other medicines

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day (see sections 4.4 and 4.5).

4.3 Contraindications

Atorvastatin is contraindicated in patients:

[…]

- treated with the hepatitis C antivirals glecaprevir/pibrentasvir

4.4 Special warnings and precautions for use

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, **tipranavir/ritonavir**, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, **antivirals for the treatment of hepatitis C (HCV)** (boceprevir, **telaprevir, elbasvir/grazoprevir**), erythromycin, niacin, **or** ezetimibe~~, telaprevir, or the combination of tipranavir/ritonavir~~. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

[…]

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). ~~Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1.~~ Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.3 and 4.4).

CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Coadministration of potent CYP3A4

inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, **some antivirals used in the treatement of HCV (e.g. elbasvir/grazoprevir)** and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

[…]

Transport ~~protein~~ inhibitors

Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

[…]

Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC[&]	Clinical Recommendation[#]

[…]

Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days	**10 mg OD for 7 days**	**8.3**	**Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).**

[…]

Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days	**10 mg SD**	**1.95**	**The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.**

[…]

5.2 Pharmacokinetic properties

Elimination

[…]

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Package Leaflet

2. What you need to know before you take atorvastatin

Do not take Atorvastatin

- **<u>If you use the combination of glecaprevir/pibrentasvir in the treatment of hepatitis C</u>**

[…]

Other medicines and atorvastatin

- Some medicines used in the treatment of hepatitis C e.g. telaprevir, **<u>boceprevir and the combination of elbasvir/grazoprevir</u>**
- Other medicines known to interact with {(Invented) name} include ezetimibe (which lowers cholesterol), warfarin (which reduces blood clotting), oral contraceptives, stiripentol (an anti-convulsant for epilepsy), cimetidine (used for heartburn and peptic ulcers), phenazone (a painkiller), colchicine (used to treat gout), **<u>and</u>** antacids (indigestion products containing aluminium or magnesium) ~~and boceprevir (used to treat liver disease such as hepatitis C)~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 August 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 October 2018