# 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 / simvastatin, the scientific conclusions are as follows:

- Lichenoid drug eruptions: Upon a review of the 8 cases identified in the MAH's safety database, 2 well-documented cases of Lichen planus were considered to be possibly causally associated with ezetimibe/simvastatin.

  Out of the 73 reports recorded in the MAHs safety database associated with simvastatin, 2 cases reported positive rechallenge and 10 positive dechallenge. The two cases (both with PT Lichen planus) with positive rechallenge are considered probably causally associated with simvastatin. In one case, positive rechallenge was recorded with reintroduction of simvastatin while in the second with reintroduction of another statin. Diagnosis in both cases was confirmed by histological examination. Out of the 10 cases reported with positive dechallenge, 2 are considered to be probably causally associated with simvastatin (both cases with PT Lichen Planus), 7 possibly (all with PT Lichen planus) and 1 conditionally (with PT Oral lichen Planus). Additionally, two well-documented literature cases are considered to be probably causally associated with simvastatin. In the first literature case, the recorded lesions resembled Lichen planus and a positive rechallenge with statin (rosuvastatin) reintroduction was recorded. In both cases, diagnosis was supported by histological examination. Currently, Lichenoid rash is already reflected in the SmPC of pravastatin. An update of the product information (SmPC section 4.8 and PL section 4) to reflect Lichenoid drug eruptions is recommended. Based on the incidence of Lichen Planus in clinical trials data available from the MAH, the frequency can be calculated as "very rare".

- Ocular events: The MAH identified a total of 358 spontaneous reports in the Eye Disorder SOC reported for ezetimibe/simvastatin and further analysis revealed n = 11 medically confirmed cases with a positive rechallenge. In two of the 11 cases (PT Vision blurred and PT Dry eyes), no concomitant medications was reported, which strongly suggests a probable causal association. For the 9 remaining medically confirmed cases with concomitant medication, the causal association is considered as at least possible. Following PTs ($n \geq 2$) Visual impairment (n=2) and Lacrimation increased (n=2) were recorded among these 9 cases.

  Additionally, the MAH identified a total of 2,300 spontaneous reports reported for simvastatin containing 2,934 events in the Eye Disorder SOC. Further analysis revealed n = 72 cases, among which 10 were medically confirmed reporting positive rechallenge and without concomitant medication and are considered probably causally associated with simvastatin. In the remaining 62 cases, the causal association is considered at least possible. Among the cases with probable and possible causal association, the most reported PTs are Vision blurred (n=16) and Visual impairment (n=9).

  Data from a retrospective study showed that statins are associated with ocular side effects, with atorvastatin and simvastatin showing a greater risk of association compared to the other statins and that the most frequently reported ocular AEs associated with were Vision blurred and Visual impairment. This is in line with the recorded cases from the MAH safety database that were considered to be at least possibly causally associated with ezetimibe/simvastatin as well as simvastatin. Currently, the SmPC of atorvastatin lists vision blurred (with frequency "uncommon") and visual disturbance (with frequency "rare") as ADRs in section 4.8; that of pravastatin vision disturbance (including blurred vision and

diplopia) (with frequency "uncommon"); that of pitavastatin visual acuity reduced (with frequency "rare"). An update of the product information (SmPC section 4.8 and PL section 4) to reflect Vision blurred and Visual impairment is justified. Based on the incidence of these events in clinical trials data available from the MAH, their frequency can be calculated as "rare".

- Muscle rupture: Upon the review of the 3 identified cases in the MAH's safety database in the reporting interval, 1 case is considered to be probably causally associated with ezetimibe/simvastatin. From the 16 cases identified in the MAH's safety database for simvastatin in the reporting interval, the LMS assessed 2 cases of muscle rupture to be probably causally associated with simvastatin, 9 possibly and 3 conditionally. The LMS additionally identified 66 cases of muscle rupture in EVDAS cumulatively. Out of the 66 cases, 4 well-documented cases not addressed by the MAH were further reviewed. Out of the 4 cases, 1 is considered to be probably causally associated with simvastatin and 3 possibly. Among the 15 cases of muscle rupture showing a possible or probable association with simvastatin therapy, in 4 cases the diagnosis of Muscle rupture was supported by use of imaging techniques (e.g. ultrasound, MRI, X-ray). Some of the cases involved persistent or significant disability or incapacity. In one case, hospitalization and surgery were required.

  Data from literature showed that the association of statin use, and muscle rupture was disproportionally present in the Netherlands Pharmacovigilance database with a ROR of 23.4 (95% CI 11.9, 46.0) and in the EudraVigilance database with a ROR of 14.6 (95% CI 12.3, 17.2). The authors additionally concluded that statin-induced muscle rupture can possibly occur without intense physical activities. This suggests that muscle rupture is potentially associated with the use of statins, including simvastatin. In addition, based on the review of available evidence on safety obtained in PSUFU procedures for atorvastatin (DE/H/PSUFU/00010347/201710/B) and rosuvastatin (NL/H/PSUFU/00002664/201711), PRAC and CMDh recommended an update of section 4.8 of the SmPC of both statins to add the ADR Muscle rupture. Therefore, an update of the product information for ezetimibe/simvastatin (SmPC section 4.8 and PL section 4) to reflect Muscle rupture is justified. Based on the incidence of Muscle rupture in clinical trials data available from the MAH, the frequency of the events can be calculated as "very rare".

- Gynecomastia: the causal association with ezetimibe/simvastatin in 3 cases (2 with positive dechallenge and 1 with positive rechallenge) is considered possible. Out of the 14 cases (6 with positive rechallenge and 8 from the time interval 15-JUL-2016 to 06-SEP-2019), 2 are considered to be probably causally associated with simvastatin, 4 possibly and 6 conditionally.

  Data from literature suggest an association between Gynecomastia and statins as a drug class. Based on biological plausibility, all statins could potentially cause this adverse reaction: a possible suppression of adrenal or gonadal steroid production due to the effect on cholesterol synthesis resulting in a high estradiol/testosterone ratio. Currently, the EU SmPC for both atorvastatin and rosuvastatin lists Gynecomastia as an ADR with frequency "very rare". An update of the product information (SmPC section 4.8 and PL section 4) to reflect Gynecomastia is justified. Based on the incidence of this event in clinical trials data available from the MAH, the frequency of the events can be calculated as "very rare".

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 / simvastatin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing ezetimibe / simvastatin 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 / simvastatin 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 4.8

Post-marketing Experience

The following additional adverse reactions have been reported in post-marketing use with ezetimibe/simvastatin or during clinical studies or post-marketing use with one of the individual components.

***Eye disorders:***

Frequency: **rare**

**vision blurred, visual impairment**

*Skin and subcutaneous tissue disorders:* […]*;*

Frequency: **very rare**

**lichenoid drug eruptions**

*Musculoskeletal and connective tissue disorders:* […];

Frequency: **very rare**

**muscle rupture**

*Reproductive system and breast disorders*

Frequency: **very rare:**

**gynecomastia**

**Package Leaflet**

Section 4

The frequency of the ADRs to be added should be given as being most appropriate in the context of the existing wording, the following proposal is based on the current PIL for Inegy (DE/H/0496/):

[…]

Additionally, the following side effects have been reported in people taking either ezetimibe/simvastatin or medicines containing the active ingredients ezetimibe or simvastatin:

[…]

- hair loss; raised red rash, sometimes with target-shaped lesions (erythema multiforme),

- **blurred vision and impaired vision (which each may affect up to 1 in 1000 people)**
- **rash that may occur on the skin or sores in the mouth (lichenoid drug eruptions) (which each may affect up to 1 in 10000 people)**

[…]

- muscle pain, tenderness, weakness or cramps; muscle breakdown; **muscle rupture (which may affect up to 1 in 10000 people)**; tendon problems, sometimes complicated by rupture of the tendon,
- **gynecomastia (breast enlargement in men) (which may affect up to 1 in 10000 people)**

## Annex III

## Timetable for the implementation of this position

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|---|---|
| Adoption of CMDh position: | November 2019 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 29/12/2019 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 27/02/2020 |