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 treprostinil, the scientific conclusions are as follows: Pain in extremity is a known adverse reaction associated with the mode of action of other prostanoids and several studies published in the literature suggested a relationship between use of treprostinil and the occurrence of this event. Based on the available data, several postmarketing cases of pain in extremity have been reported with treprostinil. In addition, pain in extremity has been reported more frequently in patients receiving treprostinil than in the placebo group in controlled clinical studies using treprostinil. As a result of this review, the PRAC considers that pain in extremity should be added to the Product Information as a common adverse reaction.

High output cardiac failure has been recognized as a dose dependent adverse reaction for prostacyclin analogue. Literature data suggested that excessive prostacyclin in persistent pulmonary hypertension can lead to a high cardiac output state. During this review, some cases of high output cardiac failure were reported with treprostinil. In all cases the dose of treprostinil was reduced due to the occurrence of the event. In two of them, the event resolved/improved following the dose reduction. In the other remaining cases, the outcome of the event was not reported and did not allow proper causality assessment but the role of treprostinil could not be ruled out. In several cases, no clear alternative etiology of high output cardiac failure was reported. In view of the available data, the PRAC considers that high output cardiac failure should be added to the Product Information as an adverse reaction with a frequency not known.

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 treprostinil the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing treprostinil 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 treprostinil 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

The following adverse reactions should be added under the SOC Musculoskeletal, connective tissue and bone disorders with a frequency **common**:

Pain in extremity

The following adverse reactions should be added under the SOC Cardiac disorders with a frequency **not known**:

High output cardiac failure

Package Leaflet

- Section 4 Possible side effects

The following adverse reactions should be added as common side effects:

Pain in the legs and/or arms

The following adverse reactions should be added as not known side effects:

Too much pumping of blood from the heart leading to shortness of breath, fatigue, swelling of the legs and abdomen due to fluid build-up, persistent cough

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