

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 epoprostenol, the scientific conclusions are as follows:

PRAC reviewed post-marketing cases indicative of high output cardiac failure in association with epoprostenol and found cases of re-challenge and de-challenge and some cases that occurred in absence of confounding medications. In addition, the PRAC considered that scientific literature indicating a close temporal relationship between the resolution of high output cardiac failure and the dose reduction of epoprostenol suggested a strong causal association. Furthermore, vasodilation resulting in compensatory increases in cardiac output is considered the most likely potential mechanisms for high output cardiac failure in association with epoprostenol.

PRAC therefore concluded that there is sufficient evidence to warrant an update to section 4.8 of the SmPC and section 4 of the PL.

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 epoprostenol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing epoprostenol 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 epoprostenol 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 reaction(s) should be added under the SOC Cardiac disorders with a frequency of not known: **high output cardiac failure**

Package Leaflet

- Section 4

Other side effects

It is not known how many people are affected by

- **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

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Adoption of CMDh position:	December 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 January 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 March 2018