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 alprostadil (indicated in peripheral arterial occlusive diseases), the scientific conclusions are as follows:

Alprostadil is a synthetic prostaglandin E1 with haemorrhealogic and vasodilatory effect and it is indicated for the treatment of stage III and stage IV chronic occlusive disease (Fontaine´s classification) in patients not eligible for revascularization or when revascularization has been unsuccessful.

Cases of "gastrointestinal haemorrhage" have been reported with the use of alprostadil. This adverse drug reaction is directly related to the known mechanism of action of alprostadil. Alprostadil has effect on platelet aggregation and the increase of blood flow might be a contributory factor leading to bleeding complications.

Based on the analysis of submitted cases with plausible temporal association (often in patients with silent form of gastrointestinal ulceration), the causality was assessed as possible.

Considering the known safety profile of alprostadil, increased reporting rate and potential seriousness of the gastrointestinal bleeding, the term "gastrointestinal haemorrhage" should be listed as an adverse drug reaction of all alprostadil-containing products indicated in peripheral arterial occlusive disease.

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 alprostadil (indicated in peripheral arterial occlusive diseases) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing alprostadil (indicated in peripheral arterial occlusive diseases) 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 alprostadil (indicated in peripheral arterial occlusive diseases) 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 **<u>underlined and in bold</u>**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.8

The following adverse reaction should be added under the SOC Gastrointestinal disorders with a frequency unknown:

<u>Gastrointestinal haemorrhage</u>

Package Leaflet

- Section 4

Frequency: Not known

<u>Bleeding from stomach and/or bowel</u>

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	April 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	9 June 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	8 August 2018