

**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 (erectile dysfunction), the scientific conclusions are as follows:

Further to the cumulative review of case reports relating to ischaemic heart disease and cerebrovascular accidents and the use of alprostadil containing products for intracavernous application, the PRAC concluded that there is an increased risk of myocardial ischaemia and cerebrovascular accidents associated with the alprostadil use in patient with risk factors for ischaemic heart disease related events and cerebrovascular accident development.

Whilst acknowledging that comorbidities associated with erectile dysfunction act as risk factors per se in ischaemic heart disease related events and cerebrovascular accident development, based on the cases identified within the cumulative analysis with plausible chronology, including fatal ones, cases with positive re-challenge, together with the fact that alprostadil for systemic use in the indication of peripheral arterial occlusive disease is known to cause myocardial infarction and cerebrovascular accident, the amendments to the sections 4.4 warnings and 4.8 undesirable effects of the summary of product characteristics (SmPC) of medicinal products for intracavernous application regarding the higher caution in patients with cardiovascular and cerebrovascular risk factors and with the ADRs “myocardial ischaemia” and “cerebrovascular accident” with the frequency “not known” are considered warranted.

Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing alprostadil for intracavernous application (erectile dysfunction), were warranted.

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 (erectile dysfunction) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing alprostadil (erectile dysfunction) for intracavernous application is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products for intracavernous application in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing alprostadil (erectile dysfunction) for intracavernous application are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

## **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~~)

*[Amendments for products for intracavernous application only]*

#### Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

**<Product name> should be used with caution in patients with cardiovascular and cerebrovascular risk factors.**

- Section 4.8

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

#### **Myocardial ischaemia**

The following adverse reaction should be added under the SOC Nervous system disorders with a frequency not known:

#### **Cerebrovascular accident**

#### Package Leaflet

- Section 2 - What you need to know before you use <Product name>

Warnings and precautions

Talk to your doctor or pharmacist before using <Product name>:

Warnings should be added as follows:

- **if you have one or more cardiovascular risk factors (these might include high blood pressure, tobacco use, raised blood glucose, raised blood cholesterol, overweight and obesity)**
  - **if you have one or more risk factors for stroke (these might include high blood pressure, raised blood cholesterol, coronary artery disease, heart arrhythmia, diabetes)**
- Section 4 - Possible side effects

The following adverse reactions should be added under with a frequency not known:

- **Insufficient blood flow to the heart muscle via the coronary arteries**
- **Stroke**

**Annex III**

**Timetable for the implementation of this position**

### Timetable for the implementation of this position

Adoption of CMDh position:	October 2016 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position :	26 November 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 January 2017