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 sulprostone, the scientific conclusions are as follows:

A total of 26 cases of hypertension in association with sulprostone administration were identified by the MAH. A search performed by the Lead Member State in Eudravigilance identified 18 cases. The analysis of the hypertension cases suggests a causal relationship between hypertension and sulprostone administration. Hypertension was associated to serious cardiac disorders, such as pulmonary oedema, in several cases. The risk appears to be high under the following circumstances: when other treatments for postpartum atonic haemorrhage were administered (oxytocine, methylergometrine, phenylephrine etc.) or when the woman had pre-existing hypertension. However, an initial flow rate of sulprostone above 100µg/h or not progressively increased (in case of insufficient therapeutic answer) was the main explanation for the occurrence of hypertension. Therefore, the risk of hypertension should be added to the product information, together with clinical recommendations to reduce the risk, such as progressive increase of sulprostone flow rate if the dose of 100µg/h is ineffective. Therefore, in view of the data presented in the reviewed PSUR(s), the PRAC considered that changes to the product information of medicinal products containing sulprostone, 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 sulprostone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing sulprostone 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 sulprostone 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 **<u>underlined and in bold</u>**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows after the warning regarding the cardiovascular risk:

<u>Since bradycardia and/or changes in blood pressure may occur, appropriate checks of the cardiac and circulatory parameters are indicated.</u>

<u>[...]</u>

<u>During post-marketing, cases of hypertension, occasionally associated with serious cardiovascular reactions, have been reported with sulprostone, especially when the initial recommended flow rate was not respected (above 100µg/h) or when the flow rate was not increased in a stepwise manner in case of insufficient therapeutic response.</u>

<u>If the flow rate needs to be increased due to insufficient treatment effect, this should be done in a stepwise manner to prevent cardiovascular complications. Resolution of the hypertension generally occurred within 30 minutes of reducing the dose or after discontinuing sulprostone.</u>

- Section 4.8

*The following adverse reaction(s) should be added under the SOC **<u>vascular disorders</u>** with a **<u>frequency not known</u>**:*

"**<u>Hypertension</u>**"

Package Leaflet

- Section 4 Possible side effects:

  <u>Blood pressure increase (frequency not known).</u>

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 May 2017