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 (patency of the ductus arteriosus), the scientific conclusions are as follows:

Hypokalaemia is considered an important identified risk, which shall be added in the product information of all alprostadil products (indicated for patency of the ductus arteriosus) due to the following reasons:

- In this PSUR reporting period, 15 serious ADRs of hypokalaemia were reported, arising from the publication by Alhussin et al. 2016, which is un-proportionally high compared to the cumulative data. The LMS is aware of the fact that 6 subjects had required additional furosemide therapy; however, the remaining 9 subjects developed hypokalaemia without concomitant furosemide.
- Causal relationship between PGE1 and hypokalaemia was shown: a significant negative correlation between serum potassium levels and PGE1 dosages was described by Tolosi G et al. 2007. Pharmacodynamics were described showing a release of nitrogen caused by protein catabolism due to the increased energy need of neonates with CCHD. The negative nitrogen balance promotes potassium secretion/excretion, which consequently results in hypokalaemia.
- According to Caballero S et al. 1998, Nadroo AM et al. 2000, and Iyu D et al. 2011 prolonged use of PGE1 results in important side effects including electrolyte disturbances.
- The healthcare professional shall be aware of all side effects (including hypokalaemia) of alprostadil, especially in long-term use, being able to weigh risks of long-term infusion of alprostadil against the possible benefits as stated in the MAH's corporate product statement for alprostadil ("the risks of long-term infusion of alprostadil (PGE1) should be weighed against the possible benefits").

The safety profile of alprostadil in the indication "patency of the ductus arteriosus" remains unchanged. Overall, based on the assessment of the interval and cumulative safety information available, the LMS considers that the benefit-risk ratio for alprostadil remains favourable for the licensed indication "patency of the ductus arteriosus".

The PRAC considers that based on the review of available data an update of the Product Information (section 4.8 of SmPC and section 4 of PL) is required concerning hypokalaemia associated with alprostadil use, in case hypokalaemia is not yet mentioned in section 4.8 of the SmPC and section 4 of the PL of the respective national product information.

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 (patency of the ductus arteriosus) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing alprostadil (patency of the ductus arteriosus) 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 (patency of the ductus arteriosus) 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:
Hypokalaemia
The frequency of the adverse reaction should be "**Common**"

Package Leaflet

4. Possible side effects "Common"

Low potassium levels in the blood (potassium deficiency)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 May 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 July 2019