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 etomidate, the scientific conclusions are as follows:

Based on results of several studies and meta-analysis investigating the effect of etomidate on mortality and morbidity in different patient populations, an association between adrenal suppression caused by etomidate use and an increased risk of mortality and morbidity in critically ill patients including patients with sepsis cannot be ruled out. Moreover, transient adrenal insufficiency has been shown to occur in all patients mainly through inhibition of 11β-hydroxylase resulting in decreased cortisol levels. Therefore, cortisol decreased should be added as an adverse reaction to the product information of etomidate-containing products with a frequency of very common. The product information should also include a warning indicating that etomidate should be used with caution in critically ill patients including patients with sepsis.

In addition, as single induction doses of etomidate can lead to transient adrenal insufficiency and decreased serum cortisol levels, statements indicating that adrenal suppression is observed only after prolonged/repeated use and that reduced cortisol levels caused by adrenal suppression have not been associated with changes in vital signs or evidence of increased mortality should be removed.

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 etomidate the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing etomidate 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 etomidate 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

- All sections

Statements that adrenal suppression is observed after prolonged/repeated use (only) and that reduced cortisol levels caused by adrenal suppression have not been associated with changes in vital signs or evidence of increased mortality should be removed.

- Section 4.4

A warning should be added as follows:

Single induction doses of etomidate can lead to transient adrenal insufficiency and decreased serum cortisol levels (see section 5.1 Pharmacodynamic properties).

Etomidate should be used with caution in critically ill patients, including patients with sepsis.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Endocrine disorders with a frequency very common:

Cortisol decreased

Package Leaflet

- All sections as applicable

Statements that adrenal suppression is observed after prolonged/repeated use (only) and that reduced cortisol levels caused by adrenal suppression have not been associated with changes in vital signs or evidence of increased mortality should be removed.

- Section 2

A warning should be added as follows:

Single induction doses of etomidate can lead to transient adrenal insufficiency and decreased serum cortisol levels.

Etomidate should be used with caution in critically ill patients, including patients with sepsis as it has been associated with in increased risk of mortality in some studies in these patient groups.

- Section 4

The following adverse reaction(s) should be added with a frequency very common:

Cortisol decreased

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	14 July 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 September 2018