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 ketamine, the scientific conclusions are as follows:

Following evaluation during the reporting interval, the signal upper urinary tract events has been determined to be an important identified risk of ketamine, subsumed under the important identified risk urinary tract-related adverse events. The marketing authorisation holder concluded that urinary tract adverse events including cystitis is a known effect associated with ketamine abuse and in advanced stage, hydronephrosis, ureteric damage and renal impairment may develop.

Considering the cumulative review performed in response to the previous Periodic Safety Update Report assessment as well as the data from this reporting period, the decision of the marketing authorisation holder to update the current Core Data Sheet and the comments from both marketing authorisation holder and Member States regarding the preliminary assessment report, it is the PRAC opinion that an association between ketamine and renal and urinary disorders cannot be excluded and most of the urinary tract events are related to ketamine abuse. Therefore, the PRAC recommends that section 4.4 of the summary of product characteristics is updated to add “acute kidney injury, hydronephrosis and ureteral disorder”.

The package leaflet and the section 4.8 of the summary of product characteristics should not be updated. The PRAC did not consider appropriate to include information on these adverse reactions in the context of abuse in the patient leaflet.

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 ketamine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing ketamine 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 ketamine 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 4.4

A warning should be revised as follows:

Long-Term Use

Cases of cystitis, including haemorrhagic cystitis, **acute kidney injury, hydronephrosis, and ureteral disorders** have been reported in patients using ketamine on a long term basis**, especially in the setting of ketamine abuse.** (~~This~~**These** adverse reactions develop in patients receiving long term ketamine treatment after a time ranging from 1 month to several years).

Hepatotoxicity has also been reported in patients with extended use (> 3 days).

Drug Abuse and Dependence

Ketamine has been reported being used as a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia, or disorientation. **Adverse effects have also been reported: see "Long-Term Use".**

~~Cases of cystitis, including haemorrhagic cystitis and cases of hepatotoxicity have also been reported.~~ Ketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, ketamine should be prescribed and administered with caution.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	8 September 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	7 November 2019