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 midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures), the scientific conclusions are as follows:

In view of available data on Kounis syndrome from spontaneous reports including four cases suggesting a plausible temporal relationship with intravenous midazolam administration and several published reviews mentioning midazolam as one of the anaesthetics that may cause Kounis syndrome, the PRAC considers a causal relationship between midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures) and Kounis syndrome is at least a reasonable possibility.

The PRAC concluded that the product information of products containing midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures) should be amended accordingly.

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 midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures) 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 midazolam (all pharmaceutical forms and indications apart from oromucosal solution indicated for the treatment of prolonged, acute, convulsive seizures) 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 <u>underlined and in bold</u>, deleted text ~~strike through~~)

Summary of Product Characteristics

• Section 4.8
The following adverse reaction should be added under the SOC Cardiac disorders with a frequency not known:

<u>Kounis syndrome*</u>

The additional note should be implemented below the table:

<u>*particularly after parenteral administration</u>

Package Leaflet

• Section 4: Possible side effects

<u>Oral formulations:</u>

[…]

<u>Immune System Disorders:</u>

<u>Hypersensitivity reactions and angioedema may occur in susceptible individuals.</u>

<u>Chest pain as a sign of a serious allergic reaction called Kounis syndrome has been observed.</u>

<u>All other pharmaceutical forms (except oral formulations):</u>

[…]

Stop having [product name] and see a doctor straight away if you notice any of the following side effects. They can be life-threatening and you may need urgent medical treatment:

- Anaphylactic shock (a life-threatening allergic reaction). Signs may include a sudden rash, itching or lumpy rash (hives) and swelling of the face, lips, tongue or other parts of the body. You may also have shortness of breath, wheezing or trouble breathing**<u>, or a pale skin, a weak and rapid pulse, or feeling of loss of consciousness. Additionally, you may experience chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.</u>**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	April 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 June 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 August 2023