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 methoxyflurane, the scientific conclusions are as follows:

In view of available data on risk from spontaneous reports and in view of a plausible mechanism of action, the Lead Member State considers a causal relationship between methoxyflurane and respiratory depression is at least a reasonable possibility.

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 methoxyflurane the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing methoxyflurane 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 methoxyflurane 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 added as follows:

Respiratory depression

Respiratory depression has been reported also from analgesic doses (section 4.8). Respiration should be monitored due to the risk for respiratory depression and hypoxia.

- Section 4.8

The following adverse reaction should be added under the SOC Respiratory, thoracic and mediastinal disorders with frequency unknown:

Respiratory depression

Package Leaflet

- Section 2 What you need to know before you use <invented name>

Warnings and precautions

[...]

Respiratory depression, with symptoms such as too slow and shallow breathing or other difficulties in breathing, has been reported in association with treatment with <invented name> (section 4). Tell your healthcare professional immediately if you experience any breathing problems.

- Section 4 Possible side effects

Tell your healthcare professional immediately if you experience any of the following:

Not known (frequency cannot be estimated from the available data)

- [...]

- **too slow and shallow breathing or other difficulties in breathing (symptoms of respiratory depression).**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December / 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29 January 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 March 2023