# 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 nitrous oxide, nitrous oxide / oxygen, the scientific conclusions are as follows:

Investigation of the signal of drug abuse revealed a significantly large body of literature and Eudravigilance (EV) cases, as evidence to support the association. The risk of addiction and abuse appears to occur with occupational, recreational use and medical use (for analgesia indication) of nitrous oxide (N2O). The majority of the EV cases (50/52) had an outcome of causality assessment as probable, highly probable or possible. Most of the cases where unconfounded, with a clear de-challenge and a positive re-challenge occurred in 1 case. The PRAC noted that in the summary of product characteristics (SmPC) of Nitrous oxide Bus Oxy there is no mention of addiction or abuse and no warning on the use of N2O in patients with a history of substance abuse.

It is noted that long-term exposure, but in some cases even short term exposure to N2O, is associated with vitamin B12 depletion, megaloblastic anaemia and spinal cord damage. According to the SmPC of Nitrous oxide Bus Oxy, megaloblastic anaemia and leukopenia are listed in section 4.8. A warning exists in section 4.8 regarding cases of suspected or confirmed vitamin B12 deficiency, or where symptoms compatible with affected methionine synthetase occur, vitamin B substitution therapy should be given. However other effects that have been described extensively in the literature are not included in the SmPC. These are subacute combined cord degeneration (supported by 40 cases in EV), neuropathy (22 cases), [Peripheral neuropathy (15 cases), polyneuropathy (7 cases)] and myelopathy (15 cases).

The PRAC considers that the risks of short and/or long term abuse of nitrous oxide and the inactivation of vitamin B12 should be presented in the SmPC of the $N_2O$ containing products.

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 nitrous oxide, nitrous oxide / oxygen the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing nitrous oxide, nitrous oxide / oxygen 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 nitrous oxide, nitrous oxide / oxygen 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**

*4.4 Special warnings and precautions for use:*

**Repeated administration or exposure to nitrous oxide may lead to addiction. Caution should be excercised in patients with a known history of substance abuse or in healthcare professionals with occupational exposure to nitrous oxide.**

**Nitrous oxide causes inactivation of vitamin B12, which is a co-factor of methionine synthase. Folate metabolism is consequently interfered with and DNA synthesis is impaired following prolonged administration of Nitrous Oxide. Prolonged or frequent use of Nitrous oxide may result in megaloblastic marrow changes, myeloneuropathy and subacute combined degeneration of the spinal cord. Nitrous oxide should not be used without close clinical supervision and haematological monitoring. Specialist advice should be sought from a haematologist in such cases.**

**Haematological assessment should include assessment for megaloblastic change in red cells and hypersegmentation of neutrophils. Neurological toxicity can occur without anaemia or macrocytosis and with vitamin B12 levels in the normal range. In patients with undiagnosed subclincial deficiency of vitamin B12, neurological toxicity has occured after single exposures to Nitrous Oxide during anaesthesia.**

*Section 4.8: Undesirable effects*

**Addiction, Myeloneuropathy, Neuropathy, Subacute degeneration of the spinal cord frequency not known**

## Annex III

## Timetable for the implementation of this position

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| Adoption of CMDh position: | February 2018 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 7 April 2018 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 6 June 2018 |