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 nefopam, the scientific conclusions are as follows:

The Pharmacovigilance Risk Assessment Committee (PRAC) agreed on the inclusion of the adverse drug reaction (ADR) “confusion state” in the product information (section 4.8) of the nefopam parenteral formulation on the basis of a known mechanism of action and a high number of serious reports received both in the reporting period, and cumulatively. In 10 of these cases nefopam was reported to be the only suspect medication, 4 of which reported a positive dechallenge and 1 reporting a positive rechallenge. Two cases reported a fatal outcome, one of which was a direct consequence of nefopam induced confusional state. Additionally, confusion is listed in the nefopam oral formulation summary of product characteristics.

The PRAC also concluded that in view of the reported cases and known anticholinergic properties of nefopam, the addition of a warning on nefopam use in patients with angle closure glaucoma in the summary of product characteristics (section 4.4) of nefopam oral formulation is warranted.

Considering the plausible mechanism of action, reviewed case reports, and known effects of nefopam overdose which can promote the onset of coma, the addition of coma in section 4.9 of the summary of product characteristics for both the oral and parenteral formulation is warranted.

Considering the presented cumulative analysis of cases reporting withdrawal symptoms and drug abuse the PRAC acknowledges that limited conclusions on nefopam oral formulation dependence and abuse can be made. However, drug abuse and dependence have been known and identified for nefopam parenteral formulation, and are adequately reflected in the SmPC under sections 4.8 and 4.4. There is also a plausible mechanism that suggests a potential for abuse and dependence by inhibition of the recapture of dopamine. On the basis of these arguments the PRAC agreed that the SmPC for the oral formulation should include a warning in section 4.4 with regards to drug abuse and dependence.

Lastly, the PRAC agreed that on the basis of the reported cases on the sudden onset of coma with usual therapeutic doses of nefopam the inclusion of the term “coma” in section 4.8 of the summary of product characteristics is warranted.

Therefore, in view of the data presented in the reviewed PSUR(s), the PRAC considered that changes to the product information of medicinal products containing nefopam were warranted.

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 nefopam the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing nefopam 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 nefopam are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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 4.8

The following adverse reaction should be added under the SOC Psychiatry disorders with a frequency not known: **confusional state**

The following adverse reaction should be added under the SOC Nervous system disorders with a frequency not known: **coma**

- Section 4.9

Symptoms: they are from anticholinergic origin: tachycardia, **coma**, convulsions and hallucinations.

Package Leaflet

- Section 4 - Possible side effects:

  Frequency not known: **coma, confusion**

Annex III / IV

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 May 2017