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 tramadol, the scientific conclusions are as follows:

In view of available data on **central sleep apnoea (CSA)** from spontaneous reports and relevant literature, the PRAC considered that a causal relationship between medicinal products containing tramadol and the risk of central sleep apnoea is at least a reasonable possibility. Therefore, the PRAC concluded the PI of products containing tramadol should be amended accordingly. (**This update is needed for MAHs which do not have similar wordings (SmPC and PL).**

In view of available data on **adrenal insufficiency** from non-clinical and clinical studies, the PRAC considered that a causal relationship between the use of tramadol and "adrenal insufficiency" is at least a reasonable possibility. Thus, PRAC concluded that tramadol PI should be amended accordingly.

Given the evidence on **hiccups** from relevant spontaneous reports and literature data, including cases with positive dechallenge, the PRAC considered that a causal relationship between the use of tramadol and hiccups is at least a reasonable possibility. Therefore, the PRAC concluded that tramadol PI 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 tramadol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing tramadol 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 tramadol 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

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

- Section 4.4

Adrenal insufficiency

Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss~~.~~

- Section 4.8

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

Package Leaflet

- Section 2. What do you need to know before you take [DRUG NAME]

Warnings and precautions

Sleep-related breathing disorders

[DRUG NAME] can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

Talk to your doctor <or> <pharmacist>< or nurse> if you experience any of the following symptoms while< taking> <using> X:

[…]

Extreme fatigue, lack of appetite, severe abdominal pain, nausea, vomiting or low blood pressure. This may indicate that you have adrenal insufficiency (low cortisol levels). If you have these symptoms, contact your doctor, who will decide if you need to take hormone supplement.

- Section 4. Possible side effects

The following possible side effects should be added:

Not known: Hiccups

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	14 March 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	13 May 2021