# 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 tapentadol, the scientific conclusions are as follows:

In total, 122 cases reporting the MedDRA preferred term (PT) delirium were identified. Based on WHO UMC criteria, 29 of them were assessed as possibly related to tapentadol. 35 as unlikely related and 58 considered unassessable/unclassifiable.

Of the 29 cases considered possibly related to tapentadol, 23 occured in elderly patients and 28 had a diagnosis of cancer. All patients were either elderly, had cancer or both. A positive dechallenge or recovery after dose reduction was observed in 18 of the 29 cases.

In tapentadol phase II and III clinical trials delirium was reported in 2 out of 2694 subjects receiving the IR tablet.

As outlined in the publication of Abeyaratne et al (2018), the Australian Health Authority received a total of 104 reports for tapentadol, and seven of them reported delirium. Furthermore, a study published by Sugiyama et al (2018) investigated 38 Japanese patients with advanced cancer receiving opioid treatment. Eighteen of these patients were switched to tapentadol, and one of them experienced delirium.

A 2017 poster presentation by Takimoto et al reported five cases of delirium observed in 23 patients with cancer pain treated in a Japanese hospital; a treatment change was required in some of these cases.

Overal, an increased risk of delirium has frequently been described in the literature for opioids as a group, mainly, but not exclusively, in cancer patients. Evidence from the published literature includes prospective and retrospective studies as well as reviews.

No new risks or (new) relevant aspects were identified for tapentadol important (identified and potential) risks and missing information.

No (new) relevant additional information on efficacy or effectiveness of tapentadol in the authorised indications became available during the reporting period covered in this PSURSA. The benefit in the approved indications can be regarded as unchanged.

In conclusion, based on review of data on safety and efficacy, the PRAC agreed that:

- The risk-benefit balance of medicinal products containing the active substance tapentadol remains favourable;
- The frequency of the PSUR submission should be revised from 1 year to 3 years.

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 tapentadol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing tapentadol 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 tapentadol 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 4.8

The following adverse reaction should be added under the SOC Psychiatric disorders with a frequency *unknown*:

**Delirium****

***Post marketing cases of delirium were observed in patients with additional risk factors such as cancer and advanced age.**

## Package Leaflet

The following adverse reaction should be added under the SOC Psychiatric disorders with a frequency unknown:

**Delirium**

## Annex III

## Timetable for the implementation of this position

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|---|---|
| Adoption of CMDh position: | July 2019 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 08 September 2019 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 07 November 2019 |