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 view of available data on the risk of opioid use disorder (OUD; including drug dependence/drug abuse) and overdose from spontaneous reports, the literature and in view of a plausible mechanism of action/class effect of opioids and taking into account the existing advice in the product information of other opioid containing products, the PRAC concluded that the product information of products containing tapentadol should be amended accordingly, including a black box warning in the product information.

In view of available data on accidental exposure from spontaneous reports and taking into account the existing warning in the product information of other opioid containing products, the PRAC concluded that the package leaflet of products containing tapentadol should be amended to highlight the need to store the product in a safe and secure place.

In view of available data on the interaction between opioids and anticholinergics from spontaneous reports, the literature and in view of a plausible mechanism of action and taking into account the existing warning in the product information of other opioid containing products, the PRAC concluded that product information of products containing tapentadol should be amended to reflect interaction with anticholinergics.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

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 recommends that the terms of the marketing authorisation(s) should be varied.

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 4.2

Method of administration

[…]

Treatment goals and discontinuation

Before initiating treatment with [product name], a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with [product name], it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

[…]

Duration of treatment

[Product name] should not be used longer than necessary.

[…]

~~Discontinuation of treatment~~

~~Withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol (see section 4.8). When a patient no longer requires therapy with tapentadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.~~

- Section 4.4

[…]

Tolerance and Opioid Use Disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids **such as [product name]**. **A higher dose and longer duration of opioid treatment can increase the risk of developing OUD**. Abuse or intentional misuse of opioids may result in overdose and/or death.
The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).
Before initiating treatment with [product name] and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

- Section 4.5

An interaction should be added as follows:

Concomitant administration of [Product name] with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

- Section 4.8

The following adverse reaction should be added under the SOC Psychiatric disorders with a frequency 'uncommon' for immediate release formulations only:

Drug dependence

The following paragraph should be added under the table of the adverse reactions:

Drug dependence

Repeated use of [product name] can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

- Section 4.9

The signs of overdose should be amended as follows:

Human experience with overdose of tapentadol is ~~very~~ limited. […] In principle, these symptoms include, referring to the clinical setting, in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions, and respiratory depression up to respiratory arrest **that may be fatal**.

Package Leaflet

- Section 2, What you need to know before you <take> <use> [product name]

[…]

Talk to your doctor or pharmacist before taking [product name] if you:

[…]

- ~~or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").~~
- ~~are a smoker.~~
- ~~have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.~~

[…]

Tolerance, dependence and addiction

This medicine contains tapentadol, which is an opioid. It can cause dependence and/or addiction.

This medicine contains tapentadol which is an opioid **medicine**. Repeated use of opioid**s** ~~painkillers~~ **can**~~may~~ result in the drug being less effective (you become accustomed to it**, known as tolerance**). **Repeated use of [product name] can** ~~It may~~ also lead to dependence**,** ~~and~~ abuse **and addiction** which may result in life-threatening overdose. **The risk of these side effects can increase with a higher dose and longer duration of use.**

~~If you have concern that you may become dependent on [product name], it is important that you consult your doctor. Use (even at therapeutic doses) may lead to physical dependence, which may result in you suffering withdrawal effects and a recurrence of your problems if you suddenly stop taking this medicine treatment.~~

~~[product name] may lead to physical and psychological addiction. If you have a tendency to abuse medicines or if you are dependent on medicines, you should only take these tablets for short periods and under strict medical supervision.~~

Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it.

The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent on or addicted to [product name] if:

- **you or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").**
- **you are a smoker.**
- **you have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.**

If you notice any of the following signs whilst taking [product name], it could be a sign that you have become dependent or addicted:

- **You need to take the medicine for longer than advised by your doctor.**
- **You need to take more than the recommended dose.**
- **You might feel that you need to carry on taking your medicine, even when it doesn't help to relieve your pain.**
- **You are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'**
- **You have made repeated, unsuccessful attempts to quit or control the use of the medicine.**
- **When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again ('withdrawal effects').**

If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely (see section 3, If you stop taking [product name]).

[…]

Other medicines and [product name]

[…]

If you use [product name] together with the below medicines that have anticholinergic effects the risk of side effects may be increased:

- **medicines to treat depression.**

- **medicines used to treat allergies, travel sickness or nausea (antihistamines or antiemetics).**
- **medicines to treat psychiatric disorders (antipsychotics or neuroleptics);**
- **muscle relaxants.**
- **medicines to treat Parkinson's disease.**

- Section 3, How to <take> <use> [product name]

Always <take> <use> this medicine exactly as your doctor <or pharmacist> has told you. Check with your <doctor> <or> <pharmacist> if you are not sure.

Before starting treatment and regularly during treatment, your doctor will discuss with you what you may expect from using [product name], when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also"If you stop taking [product name]" below).

<If you <take> <use> more [product name] than you should>

After taking very high doses, the following may be experienced:

pin-point pupils, vomiting, drop in blood pressure, fast heart beat, collapse, disturbed consciousness or coma (deep unconsciousness), epileptic fits, dangerously slow or shallow breathing or stopping breathing **which** may ~~occur~~**lead to death**.

If this happens a doctor should be called immediately!

- Section 4, Possible side effects

The following adverse reaction should be added with a frequency 'uncommon' for immediate release formulations only:

Drug dependence

- Section 5 How to store [product name]

The following information should be added. If there is existing text regarding storage recommendations (e.g. regarding temperature or locked space), add the new text directly above or directly below the existing information, as appropriate.

Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been prescribed for them.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	7 September 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	6 November 2025