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 risk(s) from the literature and recent assessments of other opioids, the PRAC considers that the product information of products containing tapentadol 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 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 4.4

A strengthened warning should be added as follows:

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. 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).
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.

Remove sentence: ~~"Potential for Abuse and Addiction/ Dependence Syndrome <TRADEMARK> has a potential for abuse and addiction. This should be considered when prescribing or dispensing <TRADEMARK> in situations where there is concern about an increased risk of misuse, abuse, addiction, or diversion.~~
~~All patients treated with active substances that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.~~

- Section 4.5

Centrally-acting medicinal products/central nervous system (CNS) depressants, including alcohol and CNS depressant narcotic drugs ~~Sedative medicines such as benzodiazepines or related drugs~~

The concomitant use of <product> with sedating medicinal products such as benzodiazepines or other respiratory or CNS depressants (other opioids, antitussives or substitution treatments, barbiturates, antipsychotics, H1-antihistamines, alcohol) increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Therefore, when a combined therapy of <product> with a respiratory or CNS depressant is contemplated, the reduction of dose of one or both agents should be considered and the duration of the concomitant use should be limited (see section 4.4). **The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.**

Package Leaflet

Section 2

What you need to know before you take/use [product name]

Warnings and precautions

Remove sentence (or similar wording) if present:

"~~If this medicine is used as intended in patients suffering from chronic pain states, the risk for physical and psychological dependence is low~~."

The following changes are recommended (if not present already):

Talk to your doctor or pharmacist before taking/using [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.

This medicine contains tapentadol which is an opioid medicine. Repeated use of opioid painkillers may result in the drug being less effective (you become accustomed to it). It may also lead to dependence and abuse which may result in life-threatening overdose. 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.

Remove sentence (or similar wording) if present:

~~Please inform your doctor if you and your family have a history of mental illness (such as depression), alcoholism or drug abuse, as the risk of dependence to [product name] could increase with the dose and length of treatment.~~

The following changes are recommended:

[…]

Sleep-related breathing disorders

[Product 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.

Remove sentence (or similar wording) if present:

~~<TRADEMARK><suffix> contains an active substance that belongs to the group of opioids. Opioids can cause sleep-related breathing disorders, for example central sleep apnea (shallow/pause of breathing during sleep) and sleep-related hypoxemia (low level of oxygen in the blood).~~
~~The risk of experiencing central sleep apnea is dependent on the dose of opioids. Your doctor may consider decreasing your total opioid dosage if you experience central sleep apnea.~~

Other medicines and [product name]

Concomitant use of [product name] and sedative medicines such as benzodiazepines or related drugs (certain sleeping pills or tranquillizers (e.g., barbiturates) or pain relievers such as opioids, morphine and codeine (also as cough medicine), antipsychotics, H1-antihistamines, alcohol) increases the risk of

drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.

However if your doctor does prescribe [product name] together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.

The concomitant use of opioids and drugs used to treat epilepsy, nerve pain or anxiety (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and may be life-threatening.

Please tell your doctor ~~about~~ **if you are taking gabapentin or pregabalin or any** ~~all~~ sedative medicines ~~you are taking,~~ and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	04 September 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	03 November 2022