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 paracetamol/tramadol, the scientific conclusions are as follows:

In view of available post-marketing case reports and literature data on the risk of drug dependency/drug abuse, and taking into account the existing warnings in other product informations of opioid containing products (notably of tramadol, one of the compound of this combination), an update of the sections 4.2, 4.4 and 4.8 of the SmPC is warranted to reinforce the labelling on the risk of drug dependency/drug abuse by adding negative consequences of opioid use disorder and risk factors identified in accordance with wordings already implemented for other opioids.

In view of available literature data on the interaction between opioids and gabapentinoids (gabapentin and pregabalin), and taking into account the existing warnings in other product informations of opioid containing products, an update of the section 4.5 of the SmPC is warranted to reflect interactions with gabapentinoids.

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 paracetamol/tramadol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing paracetamol/tramadol 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~~)

1) Updates to reinforce the warnings on the risk of drug dependency/drug abuse;

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 tramadol, 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).

- Section 4.4

A warning should be amended as follows (existing wording on the concerned warning should be replaced by the following paragraph as appropriate):

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]. Repeated use of [product name] can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of [product name] 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 4.8

The following paragraph should be added under the table or description summarising the side effects as follows:

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).

Package Leaflet

- Section 2

Existing wording on the concerned warning should be replaced by the following text highlighted in bold and underlined as appropriate.

Warnings and precautions

Tolerance, dependence, and addiction

This medicine contains tramadol which is an opioid medicine. Repeated use of opioids can result in the drug being less effective (you become accustomed to it, known as tolerance). Repeated use of [product name] can also lead to dependence, 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.

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 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]).

• Section 3.

<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 section 2).

• Section 5.

To be added directly below the sentence "Keep this medicine out of the sight and reach of children.":

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.

2) Updates to add the interactions with gabapentinoids;

Summary of Product Characteristics

• Section 4.5

An interaction should be added as follows. If identical wording is already included in SmPC section 4.5 as "The concomitant use of < product > with […], may result in respiratory depression, hypotension, profound sedation, coma or death.", the new proposed text (i.e. "gabapentinoids (gabapentin and pregabalin)") may be added to the existing sentence. If identical wording as in the previous sentence, is not already included in SmPC section 4.5, the new proposed sentence can be added directly after any existing wording on interaction with other centrally acting drugs that could result in a potentiation of CNS effects (e.g. directly after "In concomitant use of < product > and other centrally acting drugs, including alcohol, a potentiation of CNS effects should be taken into consideration (see section 4.8).").

The concomitant use of <product> with ~~other central nervous system depressants […], and~~ **gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.**

Package Leaflet

• Section 2.

To be added to an existing bullet point list in the section 'Other medicines and < product name >' (e.g. with the subheading "Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines" (or similar) or "The risk of side effects increases if you are taking" (or similar).)

Other medicines and [product name]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines

- Gabapentin or pregabalin to treat epilepsy or pain due to nerve problems (neuropathic pain)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 May 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 July 2024