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 piritramide, the scientific conclusions are as follows:

1) **Opioid Use Disorder (OUD)**

In view available data on the risk of drug abuse and dependence (opioid use disorder) from the literature and spontaneous reports and taking into account the existing warnings in other product information of opioid containing products, the PRAC considers that an update of the SmPC is warranted to reinforce the labelling on the risk of drug dependency/drug abuse and provide further information regarding **Opioid Use Disorder (OUD)** to the prescribers and patients. The PRAC considers that the product information of products containing piritramide should be amended accordingly.

2) **Interactions with gabapentinoids**

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 information of opioid containing products, the PRAC considers a causal relationship is at least a reasonable possibility. The PRAC concluded that the product information should be amended accordingly.

3) **Information on breastfeeding**

In view of available literature data on the detection of piritramide in the colostrum. The PRAC concluded that the product information should be amended accordingly to include the latest conclusions.

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 piritramide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing piritramide 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) **Opioid Use Disorder (OUD)**

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.

- Section 4.4

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

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as [product name].

Repeated use of [product name] can lead to Opioid Use Disorder (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 (eg. 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*

If the ADRs "tolerance" is already included in section 4.8 with another frequency, the existing frequency should be maintained.

The following adverse reaction should be added under the SOC General disorders and administration site conditions with a frequency "not known":

Tolerance

The following information should be added under sub section c. Description of selected adverse reactions:

Tolerance

Tolerance can develop on repeated use.

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

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

2. What you need to know before you take [product name]

Warnings and precautions

Tolerance, dependence, and addiction

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

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 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]).

3. How to take [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], in this section).

2) **Interactions with gabapentinoids**

Summary of Product Characteristics

- Section 4.5

Central nervous system (CNS) depressants CNS depressants, such as barbiturates, benzodiazepines, neuroleptics, phenothiazine derivatives, general anesthetics and other non-selective hypnotics and non-selective CNS depressants (e.g., alcohol), can enhance the respiratory depressant activity of the opioids (and also that of Dipidolor) through various mechanisms. If patients have received such CNS depressants, the Dipidolor dose will need to be reduced. Its concomitant use with Dipidolor in patients who breathe spontaneously may increase the risk of respiratory depression, deep sedation, coma, and death. **The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.**

After administration of Dipidolor, the dose of other CNS depressants should be reduced to the lowest effective dose. This is especially important after surgery, as deep analgesia is associated with pronounced respiratory depression, which can persist or reoccur during the post-surgery period. Administration of a CNS depressant, such as benzodiazepine, during this period may disproportionately increase the risk of respiratory depression.

Package Leaflet

- Section 2

<Tell your <doctor> <or> <pharmacist> if you are <taking> <using>, have recently <taken> <used> or might <take> <use> any other medicines.>

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

3) **Information on breastfeeding**

Summary of Product Characteristics

- Section 4.6

The following text (in bold) is proposed to be added to the paragraph on breastfeeding in section 4.6.

<u>Piritramide has been identified in the colostrum of women receiving piritramide treatment although at low level.</u> It is unknown whether piritramide is excreted in breast milk. However, as other opioids are known to pass into breast milk, a risk to the breastfed infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Dipidolor, taking into account the benefit of breastfeeding for the child and the benefit of treatment for the mother.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	25 January 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 March 2026