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 pethidine, the scientific conclusions are as follows:

Opioid Use Disorder (OUD)

In view of available data on the risk of opioid use disorder (OUD) from the literature, a plausible mechanism of action for pethidine, and taking into account the existing warnings in the product information of other opioid-containing products, the PRAC considers that the labelling of pethidine should reinforce the risk of drug dependence / drug abuse by adding negative consequences of OUD and risk factors, and provide further information regarding OUD to the prescribers and patients. The PRAC considers that the product information of products containing pethidine should be amended accordingly.

Sleep-related breathing disorders

In view of available data on sleep-disordered breathing from the scientific literature, a plausible mechanism of action pointing to an opioid class effect applicable for both the long- and short-term setting, and taking into account the recently added warnings for several other opioids the PRAC concluded that the product information of pethidine-containing products should be amended to include a warning on the risk of sleep-related breathing disorders.

Since there is no sufficient pethidine-specific data, currently there is no need to update the list of ADRs.

Interaction with gabapentinoids and anticholinergics / drugs with anticholinergic activity

In view of available data on risks associated with drug-drug interactions of gabapentinoids and anticholinergics / drugs with anticholinergic activity with opioids from the literature, taking into account the recently added warnings for several other opioids and in view of a plausible mechanism of action applicable for pethidine, the PRAC considers a causal relationship between pethidine and the risk of drug-drug interactions with gabapentinoids and anticholinergics / drugs with anticholinergic activity is at least a reasonable possibility. The PRAC concluded that the product information of products containing pethidine should be amended to address these interactions.

Sphincter of Oddi dysfunction and hepatobiliary disorders

In view of available data on sphincter of Oddi dysfunction from the scientific literature, a plausible mechanism of action pointing to an opioid class effect applicable for both the long- and short-term setting, and taking into account the recently added warnings for several other opioids the PRAC concluded that the product information of pethidine-containing products should be amended to include a warning on the risk of sphincter of Oddi dysfunction, and cautious use in susceptible patient groups.

Since there is no sufficient pethidine-specific data, currently there is no need to update the list of ADRs.

Hyperalgesia

In view of available data on hyperalgesia from the scientific literature, a plausible mechanism of action pointing to an opioid class effect and taking into account the recently added warnings for several other opioids the PRAC concluded that the product information of pethidine-containing products should be amended to include a warning on the risk of hyperalgesia.

Since there is no sufficient pethidine-specific data, currently there is no need to update the list of ADRs.

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

The following changes to the product information of medicinal products containing the active substance pethidine are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

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

Where there is existing text that specifies a maximum duration of use, the following wording should be added to this, rather than replace it.

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

- Section 4.4

*For the below recommendations, existing wording on the concerned warnings should be replaced by the following texts highlighted in **bold and underlined** as appropriate.*

Warnings 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 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 (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 adverse reaction should be added under the SOC "Psychiatric disorders" with a frequency "Not known":

Drug dependence

The following information should be added below the Adverse Drug Reaction table under subsection c. **Description of selected 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).

Package Leaflet

- Section 2

Warnings and precautions

Existing wordings on the concerned warnings should be replaced by the following texts highlighted in bold and underlined as appropriate.

Tolerance, dependence, and addiction

This medicine contains pethidine, which is an opioid. 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]).

- Section 3

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.>

<The recommended dose is…>

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]).

The following wording should be added regarding duration of treatment. If there is stricter wording specifying maximum duration of treatment, this should be maintained.

[Product name] should be used for the shortest duration necessary to relieve symptoms. If no effective pain relief is achieved while taking the medicine, you should seek the advice of a physician.

- Section 4

Possible side effects:

Add the adverse reaction "Drug dependence" with the frequency "Not known" (frequency cannot be estimated from the available data) as follows:

You can become dependent on [product name] (for more information see section 2 Warnings and Precautions).

Sleep-related breathing disorders

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and

sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Package Leaflet

- Section 2

Warnings and precautions

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.

Drug-drug interaction with gabapentinoids and anticholinergics / drugs with anticholinergic activity

Summary of Product Characteristics

- Section 4.5

Interactions should be added as follows:

Concomitant administration of [product name] with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Cross reference to section 4.4 should be added as applicable.

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 (see section 4.4).

Cross reference to section 4.4 should be added as applicable.

Package Leaflet

- Section 2

Warnings and precautions

Talk to your doctor if you have taken or are taking the following:

- Gabapentin or pregabalin (medicines used to treat epilepsy, nerve pain or anxiety).

[…]

- 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.

Sphincter of Oddi dysfunction and hepatobiliary disorders

Summary of Product Characteristics

- Section 4.4

Existing wording on the concerned warning should be replaced by the following ***(new text underlined and in bold,*** *deleted text ~~strike through~~) as appropriate.*

Hepatobiliary disorders

Pethidine may cause dysfunction and spasm of the sphincter of Oddi, increasing the risk of biliary tract symptoms and pancreatitis. Therefore, pethidine has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Package Leaflet

- Section 2

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> if you experience any of the following symptoms while <taking> <using> [product name]

Contact your doctor if you experience severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever as this could be symptoms associated with inflammation of the pancreas (pancreatitis) or the biliary tract system.

Hyperalgesia

Summary of Product Characteristics

If a similar wording is not already implemented, the following updates to the product information are recommended (new text **underlined and in bold,** deleted text strike through).

- Section 4.2

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 added as follows:

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of pethidine, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Package leaflet

- Section 2

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> if you experience any of the following symptoms

while <taking> <using> [product name]

You experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2026 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 May 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	9 July 2026