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 diamorphine the scientific conclusions are as follows:

In view of available data on the risk of opioid use disorders for opioids from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diamorphine and opioid use disorders is at least a reasonable possibility. The PRAC concluded that the product information of products containing diamorphine should be amended accordingly.

In view of available data on the risk of sleep-related breathing disorders for opioids from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diamorphine and sleep-related breathing disorders is at least a reasonable possibility. The PRAC concluded that the product information of products containing diamorphine should be amended accordingly.

In view of available data on the risks of opioid-induced endocrinopathies from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diamorphine and opioid-induced endocrinopathies is at least a reasonable possibility. The PRAC concluded that the product information of products containing diamorphine should be amended accordingly.

In view of available data on the risks associated with interactions with gabapentinoids and anticholinergics for opioids from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diamorphine and interactions with gabapentinoids and anticholinergics is at least a reasonable possibility. The PRAC concluded that the product information of products containing diamorphine should be amended accordingly.

In view of available data on the risks of neonatal withdrawal syndrome associated with use of diamorphine during pregnancy from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diamorphine and neonatal withdrawal syndrome is at least a reasonable possibility. The PRAC concluded that the product information of products containing diamorphine should be amended accordingly.

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

FOR PRODUCTS WITH SUBSTITUTION INDICATION ONLY:

Method of administration

[…]

Treatment goals and discontinuation

Before initiating treatment with [product name], a treatment strategy including treatment duration and treatment goals, should be agreed together with the patient. 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 (see section 4.4).

- Section 4.4

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

Warnings should be added as follows:

FOR PRODUCTS WITH PAIN INDICATION (EMERGENCY SETTING):

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 [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).

For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

FOR PRODUCTS WITH SUBSTITUTION INDICATION:

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]. 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).

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

FOR ALL PRODUCTS:

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.

FOR PRODUCTS WITH SUBSTITUTION INDICATION ONLY:

Endocrine effects

Opioids such as diamorphine may influence the hypothalamic-pituitary-adrenal or –gonadal axes, especially after long-term use. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may manifest from these hormonal changes. If an endocrine effect such as hyperprolactinaemia or adrenal insufficiency is suspected, appropriate laboratory testing is recommended and adjustment of treatment with <product name> may be considered.

- Section 4.5

Interactions should be added as follows:

FOR ALL PRODUCTS:

The concomitant use of < product > with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

Removal of existing wording in section 4.5 about interaction with anticholinergics, if present, for example: ~~*Administration of agents with antimuscarinic effects (atropine and synthetic anticholinergics) may increase the risk of severe constipation and/or urinary retention.*~~; with following amendment/addition:

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 4.6

The recommendations for use in pregnancy should be amended as follows:

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

FOR PRODUCTS WITH SUBSTITUTION INDICATION ONLY:

Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care.

- Section 4.8

FOR PRODUCTS WITH PAIN INDICATION (EMERGENCY SETTING) ONLY:

The following information should be added below ADR 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 similar wordings on the concerned warnings should be replaced by the following texts highlighted in bold and underlined as appropriate.

FOR PRODUCTS WITH PAIN INDICATION (EMERGENCY SETTING)

Tolerance, dependence, and addiction

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

This medicine contains diamorphine 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 use or how often you need to use 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 using [product name], it could be a sign that you have become dependent or addicted:

– You need to use the medicine for longer than advised by your doctor

– You need to use more than the recommended dose

- You might feel that you need to carry on using 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 using the medicine you feel unwell, and you feel better once using 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 using [product name]).

FOR PRODUCTS WITH SUBSTITUTION INDICATION:

Tolerance, dependence, and addiction

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

This medicine contains diamorphine 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.

Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to use or how often you need to use 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 using [product name], it could be a sign that you have become dependent or addicted:

– You need to use the medicine for longer than advised by your doctor

– You need to use 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 using the medicine you feel unwell, and you feel better once using 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 using [product name]).

Warnings and precautions

FOR ALL PRODUCTS:

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.

FOR PRODUCTS WITH SUBSTITUTION INDICATION ONLY:

<Product name>, like other opioids, may affect the normal production of hormones in the body such as cortisol, prolactin, or sex hormones, particularly if you have used <product name> for long periods of time. The effects of these hormonal changes may include feeling or being sick (including vomiting), loss of appetite, tiredness, weakness, dizziness, low blood pressure, infertility, or decreased sex drive. In addition, female patients may experience changes in menstrual cycle, while male patients may experience impotence or enlarged breasts. If you notice any of these signs, speak to your doctor.

Other medicines and [product name]

FOR ALL PRODUCTS:

In case not already included in the current Package Leaflet, the following other medicines should be added/ amended:

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

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

[…]

- 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;

Pregnancy <and breast-feeding>

For the below recommendations, existing similar wordings on the concerned warnings should be replaced by the following text highlighted in bold and underlined, as appropriate.

FOR PRODUCTS WITH SUBSTITUTION INDICATION ONLY:

If <Product name> is used during pregnancy, there is a risk of the new-born child having drug withdrawal (abstinence) symptoms (such as high-pitched crying, irritability and trembling) which should be treated by a doctor.

- Section 3.

How to use [product name]

FOR PRODUCTS WITH SUBSTITUTION INDICATION ONLY:

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 use it, when to contact your doctor, and when you need to stop it (see also, If you stop using [product name]).

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