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 morphine, morphine/cyclizine, the scientific conclusions are as follows:

- In view of available data on **acute generalised exanthematous pustulosis (AGEP)** from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between morphine, morphine/cyclizine and AGEP is at least a reasonable possibility. The PRAC concluded that the product information of products containing morphine, morphine/cyclizine should be amended accordingly.
- In view of available data on **increased risk of respiratory depression with concomitant treatment with gabapentin or pregabalin** from the literature and in view of a plausible mechanism of action, the PRAC considers a causal relationship between morphine, morphine/cyclizine and increased risk of respiratory depression with concomitant treatment with gabapentin or pregabalin is at least a reasonable possibility. The PRAC concluded that the product information of products containing morphine, morphine/cyclizine should be amended accordingly.
- In view of available data on **central sleep apnoea** from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between morphine, morphine/cyclizine and central sleep apnoea is at least a reasonable possibility. The PRAC concluded that the product information of products containing morphine, morphine/cyclizine should be amended accordingly.
- In view of available data on **pancreatitis/spasm of sphincter of Oddi** from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between morphine, morphine/cyclizine and pancreatitis/spasm of sphincter of Oddi is at least a reasonable possibility. The PRAC concluded that the product information of products containing morphine, morphine/cyclizine should be amended accordingly.
- In view of literature reports and previous actions taken for other opioid products, the PRAC considers that further information regarding **Opioid Use Disorder (OUD)** should be communicated to the prescribers and patients. The PRAC concluded that the product information of products containing morphine, morphine/cyclizine 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 morphine, morphine/cyclizine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing morphine, morphine/cyclizine 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 morphine, morphine/cyclizine 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

For products with pain indication:

- 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.

For products with substitution indication:

- 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, 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).

Duration of treatment

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

For all products:

- Section 4.4

A warning should be added as follows:

Special warnings and precautions for use

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.

[…]

Severe cutaneous adverse reactions (SCARs)

Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.

If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

[…]

Hepatobiliary disorders

Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.

[…]

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 behavior (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 4.5

For SmPCs that do not already have the below wording on the topic, the following interaction should be added as follows:

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anaesthetics, phenothiazines, other tranquilisers, muscle relaxants, antihypertensives, **gabapentin or pregabalin** and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine.

- Section 4.8

Table of ADRs:

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency not known:

Acute generalised exanthematous pustulosis (AGEP)

The following adverse reaction should be added under the SOC Respiratory disorders with a frequency not known:

Central sleep apnoea syndrome

The following adverse reactions should be added under the SOC Gastrointestinal disorders with a frequency not known:

Pancreatitis

The following adverse reactions should be added under the SOC Hepatobiliary disorders with a frequency not known:

Spasm of sphincter of Oddi

MAHs with the above-mentioned adverse reactions already included in their product information section 4.8 should maintain their calculated frequency.

The following information should be added under sub section 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

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

Tolerance, dependence, and addiction

This medicine contains morphine 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]).

Warnings and precautions - Take special care with [Product name]:

Acute generalized exanthematous pustulosis (AGEP) has been reported in association with [Product name] treatment. Symptoms usually occur within the first 10 days of treatment. Tell your doctor if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking [Product name] or other opioids. Stop using [Product name] and seek medical attention immediately, if you notice any of the following symptoms: blistering, widespread scaly skin or pus-filled spots together with fever.

[…]

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.

[…]

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) and the biliary tract system.

Other medicines and [product name]

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

A large number of drugs can interact with Morphine Sulfate Injection which can significantly alter their effects. These drugs include:

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

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 following sentence is applicable for morphine-containing products with an authorised indication for treatment of pain)

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).

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using [product name] and seek medical attention immediately if you notice any of the following

symptoms:

Severe skin reaction with blistering, widespread scaly skin, pus-filled spots together with fever. This could be a condition called Acute Generalized Exanthematous Pustulosis (AGEP).

Other possible side effects:

Not known (frequency cannot be estimated from the available data)

- **Sleep apnoea (breathing pauses during sleep)**

Symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system, e.g. severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	06 August 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	05 October 2023