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 hydromorphone, the scientific conclusions are as follows:

In view of available data on the interaction with gabapentinoids (gabapentin and pregabalin) from clinical trials and the literature, the PRAC considers that an adverse interaction between hydromorphone and gabapentinoids (gabapentin and pregabalin) is established. The PRAC concluded that the product information of products containing hydromorphone should be amended accordingly.

In view of available data on drug abuse and dependence (opioid use disorder) from the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC considers that existing warning on drug dependence and potential for abuse should be amended.

In view of the available data on the risk of central sleep apnoea (CSA) from the literature and spontaneous reports, including three at least possible hydromorphone-specific cases reporting central sleep apnoea, as diagnosed with polysomnography, showing a close temporal relationship of which two showed a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between hydromorphone and central sleep apnoea is at least a reasonable possibility and Product Information should be updated 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 hydromorphone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing hydromorphone 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 hydromorphone 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

- Section 4.4

A strengthened warning 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.

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).

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.

Remove sentence (or similar wording) if present: *"~~However, when used as intended in patients with chronic pain the risk of developing physical or psychological dependence is markedly reduced~~"*

Remove sentence (or similar wording) if present: *"~~There are no data available on the actual incidence of psychological dependence in chronic pain patients~~"*

Remove sentence (or similar wording) if present: *"~~Hydromorpone has an abuse profile similar to other strong opioid agonists and may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including hydromorphone. [Product name] should be used with particular care in patients with a history of alcohol or drug abuse.~~*

- 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 manner (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

- Section 4.5

The interactions should be amended as follows:

Central nervous system (CNS):

~~Sedative medicines such as benzodiazepines or related drugs:~~ The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, hypnotics and sedatives (incl. benzodiazepines), antipsychotics, anaesthetics (e.g. barbiturates), antiemetics, antidepressants, antihistaminic drugs, phenothiazines and alcohol. Alcohol may also enhance the pharmacodynamic effects of hydromorphone; concomitant use should be avoided.

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

- Section 4.8

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

Central sleep apnoea syndrome

Package Leaflet

- Section 2. What you need to know before you take/use [hydromorphone-containing product]

Warnings and precautions

Remove sentence (or similar wording) if present:

"~~If this medicine is used as intended in patients suffering from chronic pain states, the risk for physical and psychological dependence is low~~."

The following changes are recommended:

Talk to your doctor or pharmacist before taking/using [product name] if you:

[…]

~~- are or have ever been addicted to alcohol or drugs, or have a known opioid dependence;~~

- 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.**

This medicine contains hydromorphone which is an opioid medicine. Repeated use of opioid painkillers may result in the drug being less effective (you become accustomed to it).

Repeated use of [product name] may lead to dependence and abuse which may result in life-threatening overdose. If you have concern that you may become dependent on [product name], it is important that you consult your doctor.

Concomitant use of [product name] and benzodiazepines (that can help to reduce anxiety and seizures, relax the muscles, and induce sleep) increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered

when other treatment options are not possible. **The concomitant use of opioids and drugs used to treat epilepsy, nerve pain or anxiety (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and may be life-threatening.**

Sleep-related breathing disorders

[Product name] can cause sleep-related breathing disorders such as sleep apnea (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.

- Section 4. Possible side effects

Frequency not known:

Sleep apnoea (breathing pauses during sleep)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	04 Sep 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	03 Nov 2022