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 risks of opioid use disorder from the literature, spontaneous reports, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between hydromorphone and risks of opioid use disorder is at least a reasonable possibility. The PRAC concluded that the product information of products containing hydromorphone 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 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 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~~)

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.

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 hydromorphone, 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:
Hydromorphone should not be used longer than necessary

- Section 4.4

Opioid Use Disorder (abuse and dependence):
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as hydromorphone.

-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.

- Section 4.8

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

A black box warning should be added directly under the subheading 'Tolerance, dependence and addiction', as follows:

Tolerance, dependence and addiction

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

This medicine contains hydromorphone which is an opioid medicine. Repeated use of opioid painkillers 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> <use> or how often you need to <take> <use> it.

The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent or addicted on {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> <using> {product name}, it could be a sign that you have become dependent or addicted:

– You need to <take> <use> the medicine for longer than advised by your doctor.

– You need to <take> <use> more than the recommended dose.

– You might feel that you need to carry on <taking> <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 <taking> <using> the medicine you feel unwell, and you feel better once <taking> <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 <taking> <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

APPENDIX I

PRAC PSUR Assessment Report