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 oxycodone hydrochloride / paracetamol, the scientific conclusions are as follows:

In view of available information about medicines of the same therapeutic class, including oxycodone, and based on a strong mechanistic plausibility overall leading to updates of the Product Information for other opioids, the PRAC considers that the conclusion drawn for oxycodone are applicable also to the fixed dose combination of oxycodone hydrochloride/paracetamol; the PI should be amended to include an update of section 4.4 of the SmPC to add a warning about Hepatobiliary disorders including Sphincter of Oddi dysfunction, and update of section 4.8 of the SmPC to add the adverse reaction Sphincter of Oddi dysfunction with a frequency Not known. The Package leaflet is updated accordingly.

In view of the scientific consensus in the medical practice about the need for establishing treatment goals and discontinuation plan as well as for educating the patient about the risk and signs of OUD before and during treatment (Hauser et al 2021, Dowell et al 2016), regular reassessment during opioid treatment is needed considering potential changes in the B/R balance over time at patient level. To further create awareness among patients and carers the patient leaflet has been updated with OUD signs based on DSM-5 Criteria for Substance Use Disorders.

Further, two large observational studies from the US (Edlund et al. 2014) and the UK (Bedson et al. 2019) showed that a higher dose and longer duration of opioid treatment were associated with an increased risk of developing OUD. The PRAC considers that these evidence for opioids in general has also relevance for the oxycodone hydrochloride/paracetamol fixed dose combination.

Regarding toxic leukoencephalopathy, in view of available data from literature including 7 adult literature cases with a close temporal relationship following an overdose with oxycodone and/or a positive de-challenge (Jones et al 2020; Middelbrooks et al 2016; Holyoak 2014; Koya et al 2014; Morales et al 2010; Ung et al 2021), the PRAC considers that the conclusion of causal relationship between oxycodone and toxic leukoencephalopathy as an acute overdose symptom has also relevance for the oxycodone hydrochloride/paracetamol fixed dose combination.

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 oxycodone hydrochloride / paracetamol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing oxycodone hydrochloride / paracetamol 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

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 oxycodone, 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).

~~If long-term or repeated treatment is necessary therapy pause should be considered, and patients should be carefully and regularly monitored .~~
~~In any case, abrupt therapy discontinuation should be avoided; it may be advisable to taper the dose gradually (see Section 4.4).~~

…

- 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 oxycodone. ~~Iatrogenic addiction following therapeutic use of opioids is known to occur.~~

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 4.4**

[…]

Hepatobiliary disorders

Oxycodone may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, oxycodone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

[…]

- Section 4.8

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).

● Section 4.8

The following adverse reaction(s) should be added under **the SOC Hepatobiliary disorders** with a frequency **Not known:**

Sphincter of Oddi dysfunction

- Section 4.9

The signs and symptoms of overdose should be added as follows:

Toxic leukoencephalopathy has been observed with oxycodone overdose.

Package Leaflet

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

Warnings and precautions

Tolerance, dependence and addiction

This medicine contains oxycodone 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.** ~~If you have concern that you may become dependent on [product name], it is important that you consult your doctor.~~

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. You might feel that you need to carry on taking your medicine, even when it doesn't help to relieve your pain.

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 {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}).

● Section 2

Talk to your doctor or pharmacist before taking <product> if you:

● have inflammation of the pancreas (which may cause severe pain in the abdomen and back), problems with your gall bladder or bile duct;

● have colicky abdominal pain or discomfort;

[...]

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.

[...]

- Section 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.>

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}).

- Section 3. How to take [product name]

...
If you take more [product name] than you should or if someone accidentally swallows your capsules
...
An overdose may result in:
…
– A brain disorder (known as toxic leukoencephalopathy)

- **Section 4**

The following adverse reaction(s) should be added with a frequency **Not known:**

A problem affecting a valve in the intestines that may cause severe upper abdominal pain (sphincter of Oddi dysfunction)

- **PIL Section 5. How to store [product name]**

Keep this medicine out of the sight and reach of children. **Store this medicine in a locked safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been prescribed for them.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	7 April 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	6 June 2024