# 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, the scientific conclusions are as follows:

Following a trend analysis by the brand leader MAH in the EEA (+UK) between 2011 and 2020 showing a two-fold increase in number of reported oxycodone cases related to MedDRA SMQ "Abuse, drug dependence and withdrawal" in the past 5 years (2016-2020) as compared to the previous 5 years (2011-2015), taking exposure into account, the PRAC is of the opinion that the addition of a strengthened label regarding risk of opioid use disorders in the Product Information of all oxycodone hydrochloride containing products is warranted.

In view of the available data on the risk of central sleep apnoea (CSA) from the literature and spontaneous reports, including at least three possible oxycodone-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 oxycodone and central sleep apnoea is at least a reasonable possibility. Furthermore, a meta-analysis by Correa et al. (2015) showed an overall high prevalence of CSA (24%) in patients taking chronic opioids as well as a dose-response relation with severity of CSA based on morphine equivalent daily dose. A meta-analysis by Filiatrault et al. (2016) confirmed that opioid use was significantly associated with a medium increase in central apnoea indices. There is also some evidence that opioids may potentially contribute to sleep related hypoxemia, but this link is considered less evident as compared to central sleep apnoea due to absence of oxycodone-specific cases.

Since in the EEA the oral and parenteral (i.v./ s.c.) formulations of oxycodone both have the indication of treatment of severe pain, allowing non-acute use, the above Product Information updates are recommended for all formulations of the products containing oxycodone as included in current PSUSA.

The PRAC concluded that the Product Information of products containing oxycodone (all formulations) 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 oxycodone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing oxycodone 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 oxycodone 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:

***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] may lead to Opioid Use Disorder (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).***

***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.***

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: *"~~Oxycodone 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 oxycodone. [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 fashion. In patients who present with CSA, consider decreasing the total opioid dosage.***

- Section 4.8

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

***Central sleep apnoea syndrome***

Note that the term 'Central sleep apnoea syndrome' (MEDdra LLT) as ADR to be added is preferred over 'Sleep apnoea syndrome' (PT), as 'Central sleep apnoea syndrome' more precisely reflects the case narratives identified in the safety database of brand leader MAH Mundipharma, and should be listed under SOC Respiratory, thoracic and mediastinal disorders since this is the primary SOC. The frequency category proposed to Central sleep apnoea syndrome (not known) is based on the frequency assigned to this ADR in the current CCDS of brand leader MAH.

**Package Leaflet**

Note: depending on formulation (e.g., capsules or injection) "*taken"* (capsules) or "*used"* (injections) should be used.

-Regarding Opioid Use Disorder:

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

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.***

*[…]*
***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.***

-Regarding sleep apnea:

- Section 2. What you need to know before you take [oxycodone-containing product]

Warnings and precautions

***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***.

- 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**

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|---|---|
| Adoption of CMDh position: | December 2021 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 30 January 2022 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 31 March 2022 |