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:

Sphincter of Oddi dysfunction can involve the biliary sphincter and/or the pancreatic sphincter which may lead to, respectively, a dilated common bile duct and/or a dilated pancreatic duct (McLoughlin et al. 2007, Afghani et al. 2017). Therefore, the current warning regarding hepatobiliary disorders in the SmPC of oxycodone/paracetamol requires modification, by removing "..raising intrabiliary pressure..". There is no need to change the package leaflet (PL), since a reference to raised intrabiliary pressure is not included in the PL.

Opioid-Induced Hyperalgesia (OIH) has been described as a paradoxical response whereby opioid administration induces an increase in pain sensitivity rather than an analgesic effect. Although the exact mechanisms of OIH are still not clear, several evidences strongly support the implication of activation of amino acid receptors such as the N-methyl-D-aspartate receptor (NMDAR) in this phenomenon. Recent non-clinical observations (Han et al, 2024) show that OIH could be driven by hyperpolarization-activated, cyclic nucleotide-gated (HCN2) ion channels in peripheral nociceptors. A causal relation between oxycodone and hyperalgesia has been already established. This issue is considered to have relevance also for oxycodone/paracetamol fixed dose combination (FDC).

Dependence and addiction are important risks of oxycodone and remain of concern in the EU/EEA. From literature, several published studies confirm increasing use of opioid-containing medicines in the EU/EEA, although trends may vary across individual member states (e.g., Kalkman et al. 2019, Häuser et al. 2020, Pierce et al. 2021). There are signals of problematic chronic and/or high dose opioid use in EU (e.g., Ellerbroek et al. 2024, Schrader et al. 2024, Vincent et al. 2024). In a recent cross-sectional survey study in the Netherlands (e.g., Jansen-Groot Koerkamp et al. 2024), among general practitioners' and community pharmacists, the majority of respondents agreed that too many opioids are used in the treatment of chronic non-malignant pain and that there are concerns about the addictive potential of opioids. There is also evidence suggesting that in some EU/EEA countries there is increase in opioid-related harm (e.g., di Gaudio et al. 2021, Häuser et al. 2020, Pierce et al. 2021). This consideration for oxycodone, leading to an update of the Package Leaflet in the recently finalised PSUSA procedure for oxycodone mono component (PSUSA-00002254-202404) has also relevance for the oxycodone hydrochloride/paracetamol FDC.

The PRAC concluded that the product information of medicinal products containing oxycodone/paracetamol 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 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 4.4

A warning should be amended as follows:

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 adverse reaction(s) should be added under the SOC Nervous system disorders with a frequency Not known:

Hyperalgesia

Package Leaflet

- Section 2

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

Tolerance, dependence and addiction

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

This medicine contains oxycodone which is an opioid medicine. Repeated use etc..

- Section 4

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

abnormally increased sensitivity to pain

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	16 March 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	15 May 2025