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:

Considering the 8 oxycodone-specific cases reporting Sphincter of Oddi Dysfunction (SOD) (4 probable and 4 possible cases) and 1 oxycodone-naloxone case reporting SOD (1 possible), the plausible mechanism reported in the literature describing opioid-induced spasms of the sphincter (e.g., Voorthuizen et al. 2000, and Thompson et al. 2001), the PRAC considers a causal relationship between oxycodone and SOD is at least a reasonable possibility.

Several strong post-marketing cases were identified. Among the 8 oxycodone-specific cases of SOD there were 4 probable cases; 2 cases had a time to onset (TTO) of 1 day, 1 case a TTO of 18 days, and 1 overdose case from literature involving an infant a TTO of < 1 day (González et al. 2020). The latter infant overdose case also reported pancreatic disorder, lipase and amylase increased, which is suggestive for (acute) pancreatitis, while the other 3 probable SOD cases did not report (acute) pancreatitis. All 4 probable cases had a positive de-challenge, and in 3 of them the reporters explicitly concluded on a probable or reasonable relation, or pointed out the absence of other causative factors. The remaining 4 SOD cases were considered possible cases with time to onset (TTO) of respectively 1 day, 1 day, 11-16 days (Yamada et al. 2009), and ~1 year (Kumakura et al. 2020), of which 2 cases also reported (acute) pancreatis. Of the above 8 SOD cases, 4 SOD cases explicitly mentioned pain (acute/ biliary / in attack) in abdominal or hypochondrial region. The final case was a user of an oxycodone-naloxone combination product, with a TTO < 1 day, and positive de-challenge but brief narrative, and therefore considered a possible case.

Regarding acute pancreatitis (AP), in addition to the 3 SOD cases above, also reporting events suggestive for AP (1 probable infant overdose case and 2 possible cases), there were 2 additional possible cases reporting (acute) pancreatitis, but not reporting SOD. Both cases had a TTO of ~1 day and a positive de-challenge, but one case was confounded by sepsis— pancreatic injury is common in septic shock (Chaari et al 2016)—, and the other case concerned an adult overdose case without specific information about whether there were other medications used excessively concomitantly or in the past, and with confounding factor: celiac disease which is linked to the development of pancreatitis (Sadr-Azodi et al. 2012). Considering the total of *3 possible* non-overdose cases reporting AP, but the absence of *probable* non-overdose cases, the PRAC considers there is insufficient evidence to definitely conclude on a causal relationship between (on-label) oxycodone use and AP, but the addition of a warning is considered justified. This is further supported by a plausible underlying mechanism (possibility of pancreatitis secondarily to SOD).

Considering the above, the PRAC concluded that the product information of products containing oxycodone 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 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 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

Oxycodone has to be administered with caution in patients with:

…Pancreatitis…Diseases of the biliary tract…

[…]

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 Hepatobiliary disorders with a frequency *Not known*:

Sphincter of Oddi dysfunction

Package Leaflet

• 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 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)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	24 December 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	22 February 2024