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 naloxone / oxycodone, the scientific conclusions are as follows:

In view of available data on hepatobiliary disorders from the literature, spontaneous reports including in 8 oxycodone and 1 oxycodone/naloxone cases a close temporal relationship, a positive de-challenge in 5 of these cases and in view of a plausible mechanism of action, the PRAC considers a causal relationship between naloxone/oxycodone as per EURD list and hepatobiliary disorders including sphincter of Oddi dysfunction is at least a reasonable possibility. The PRAC concluded that the product information of products containing naloxone/oxycodone should be amended accordingly.

In view of available data on interactions of opioids with anticholinergics and taking into account the existing information in the summary of product characteristics (SmPC) and package leaflet (PL) of other opioid containing products, including oxycodone (single active substance authorisations), the PRAC considers that the conclusions drawn for oxycodone are applicable also to the fixed dose combination of naloxone/oxycodone. The PRAC concluded that the product information of products containing naloxone/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 naloxone / oxycodone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing naloxone / 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

~~Biliary tract disorders~~
~~Oxycodone can cause an increase in intrabiliary pressure and spasm as a result of its effects on the sphincter of Oddi; therefore, patients with diseases of the biliary tract should be monitored for worsening symptoms while administering oxycodone.~~

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

- Section 4.5

Concomitant administration of oxycodone with anticholinergics or medications with anticholinergic activity (e.g. tri-cyclic antidepressants, antihistamines, anti-psychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Package Leaflet

- Section 2

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) or the biliary tract system.

With regard to information on interactions with anticholinergics, the following text should be added to the PL if these or similar wording are not already implemented:

Tell your doctor if you are taking:
- **medicines to treat depression;**
- **medicines used to treat allergies, travel sickness or nausea (antihistamines or antiemetics);**
- **medicines to treat psychiatric disorders (antipsychotics or neuroleptics);**
- **muscle relaxants;**
- **medicines to treat Parkinson's disease;**

- Section 4 (subsection on active substance oxycodone)

frequency not known: problems with bile flow, ~~Sphincter of Oddi dysfunction (a condition that affects normal functioning of the bile duct)~~ **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:	April 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	09 June 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	08 August 2024