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 methadone, the scientific conclusions are as follows:

In view of available data on sphincter of Oddi dysfunction as a class effect for opioids, the PRAC considers a causal relationship between methadone and sphincter of Oddi dysfunction is at least a reasonable possibility. The PRAC concluded that the product information of products containing methadone should be amended accordingly.

In view of available data on hyperalgesia from the scientific literature, the PRAC considers a causal relationship between methadone and hyperalgesia is at least a reasonable possibility. The PRAC concluded that the product information of products containing methadone indicated in the treatment of pain should be amended accordingly.

In view of available data on examining congenital malformations and neurodevelopmental impairment in children born to opioid-dependent mothers from the scientific literature and observational studies, the PRAC considers a causal relationship between methadone exposure and congenital malformations and neurodevelopmental impairment in children born to opioid-dependent mothers is at least a reasonable possibility. The PRAC concluded that the product information of products containing methadone should be amended to reflect the available evidence.

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 methadone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing methadone 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~~)

Sphincter of Oddi dysfunction and hepatobiliary disorders

Summary of Product Characteristics

- Section 4.4

Existing wording on the concerned warning should be replaced by the following ***(new text underlined and in bold****, deleted text* ~~*strike through*~~*) as appropriate.*

Hepatobiliary disorders

Methadone may cause dysfunction and spasm of the sphincter of Oddi, increasing the risk of biliary tract symptoms and pancreatitis. Therefore, methadone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

- Section 4.8

The following adverse reaction should be added under the SOC Hepatobiliary disorders with a frequency not known:

sphincter of Oddi dysfunction

The following adverse reaction should be added under the SOC Gastrointestinal disorders with a frequency not known:

acute pancreatitis

Package leaflet:

- Section 2

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> if you experience any of the following symptoms while <taking> <using> [product name]

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.

- Section 4

Other possible side effects:

Not known (frequency cannot be estimated from the available data)

Symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system (a problem affecting a valve in the intestines known as sphincter of Oddi dysfunction), e.g. severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever.

Hyperalgesia

Summary of Product Characteristics

If a similar wording is not already implemented, the following updates to the product information are recommended (new text **underlined and in bold**, deleted text strike through).

Section 4.2

In absence of adequate pain control, the possibility of **hyperalgesia,** tolerance and progression of underlying disease should be considered (see section 4.4).

Section 4.4

A warning should be added as follows:

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of methadone, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

Package leaflet:

- Section 2

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> if you experience any of the following symptoms while <taking> <using> [product name]

Pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine.

Use in Pregnancy

Summary of Product Characteristics

- Section 4.6

Any existing wording indicating that there is no association or insufficient evidence of an association with congenital malformations should be replaced with the following paragraph (new text **underlined and in bold**).

Some observational studies have reported congenital malformations and neurodevelopmental impairment in children born to women treated with methadone for opioid use disorder during pregnancy. However, due to study limitations and confounding by maternal, familial and socioenvironmental factors associated with opioid use disorders no conclusions can be drawn regarding the contribution of methadone.

Package leaflet:

Section 2

Pregnancy, breast-feeding and fertility

Some studies have reported birth defects or neurodevelopmental problems (problems with early childhood development) in children born to mothers who used methadone during pregnancy to treat opioid addiction. However, it is not possible to determine if this is caused by methadone use or other factors such as the health of the mother and social and environmental conditions associated with opioid addiction.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2026 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	15 March 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	14 May 2026