# 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 levomethadone , the scientific conclusions are as follows:

As part of the parallel PSUSA procedure and in line with recent updates to product information for other opioids, some changes to the SmPC for methadone were requested. As methadone is a racemic mixture of levomethadone and dextromethadone, it is considered justified to implement the changes for levomethadone as well.

In view of available data on drug abuse and dependence (opioid use disorder) from the literature and recent assessments of other opioids PSUSAs, the PRAC considers that the existing warning on drug dependence and potential for abuse should be further strengthened. Dependence is not reflected consistently in section 4.8 of the various national SmPCs. Dependence should be reflected in section 4.8 under the SOC Psychiatric disorders of all SmPCs. No frequency for dependence can be calculated based on the available data. Therefore, where no frequency is currently listed, dependence should be added with a frequency of 'not known'.

In view of available data on accidental ingestion in the paediatric population, the PRAC further considers that amendments to the package leaflet are warranted in order to highlight the potential serious consequences of accidental ingestion and the importance of appropriate storage.

Furthermore, based on data from post-marketing case reports and the literature, and taking into account the existing reflections in other product information, the PRAC considers that updates to section 4.5 of the SmPC are warranted to reflect interactions with gabapentinoids and cannabinoids, with corresponding updates in the PL.

In view of available data on toxic leukoencephalopathy, in the context of methadone overdose from the literature, the PRAC considers that updates to section 4.9 are warranted to reflect this as a symptom of acute overdose.

The PRAC further considers that given the available data on the risk of central sleep apnoea (CSA) from the literature and spontaneous reports, and a plausible mechanism of action, that a causal relationship between levomethadone and central sleep apnoea is a reasonable possibility and considers that updates to section 4.4 and 4.8 of the SmPC with corresponding updates to the PL are warranted.

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 levomethadone the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing levomethadone 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 levomethadone 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 4.2 (*where levomethadone has an authorised indication for treatment of pain*)

*Method of administration*

*…*

***Treatment goals and discontinuation***

***Before initiating treatment with [product name], a treatment strategy including treatment duration and treatment goals should be agreed together with the patient in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with levomethadone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4). In absence of adequate pain control, the possibility of tolerance and progression of underlying disease should be considered (see section 4.4).***

Section 4.4 (*all marketing authorisations, unless otherwise stated*)

~~*Addiction/Tolerance/Dependence*~~ ***Opioid Use Disorder (abuse and dependence)***

*Levomethadone is* ***an opioid*** ~~*a narcotic*~~ *analgesic and is highly addictive in its own right. It has a long half-life and can therefore accumulate. A single dose which will relieve symptoms may, if repeated on a daily basis, lead to accumulation and possible death.*

~~*Tolerance and dependence may occur as with morphine.*~~

***As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of levomethadone.***

*(The following two paragraphs are applicable where levomethadone has an authorised indication for treatment of pain)*

***When used for the treatment of pain, repeated use of [product name] can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD.***

***Before initiating treatment with [product name] and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.***

***Abuse or intentional misuse of [product name] may result in overdose and/or death.***

***The risk of developing Opioid Use Disorder 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 behaviour (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.***

***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 4.5

An interaction should be added as follows:

***The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.***

…..

**Cannabidiol**

**Concomitant administration of cannabidiol may result in increased plasma concentrations of methadone.**

Section 4.8

SOC Respiratory, Thoracic and Mediastinal Disorders:

***Central sleep apnoea syndrome (with frequency category Not known).***

SOC Psychiatric Disorders:

**Dependence (with frequency category *Not known* unless other frequency already stated).**

Section 4.9

***Toxic leukoencephalopathy has been observed with methadone overdose***

**Package Leaflet**

Section 2.
Warnings and precautions

~~*You should be aware that prolonged use of levomethadone can result in tolerance of the drug and both physical and psychological addiction to levomethadone. If you have any concerns speak to your doctor before you are given this medicine*~~

***Tolerance, dependence, and addiction***

***This medicine contains levomethadone which is an opioid medicine. Repeated use of opioids can result in the drug being less effective (you become accustomed to it, known as tolerance). Repeated use of [product name] can also lead to dependence, abuse, and addiction, which may result in life-threatening overdose.*** *(The following sentence is applicable*

*where levomethadone has an authorised indication for treatment of pain)* ***The risk of these side effects can increase with a higher dose and longer duration of use.***

***Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it.*** *(The following sentence is applicable where levomethadone has an authorised indication for treatment of pain)* ***When used for the treatment of pain, you might feel that you need to carry on taking your medicine, even when it doesn't help to relieve your pain***

***The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent or addicted on {product name} if:***

***- 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.***

***If you notice any of the following signs whilst taking {product name}, it could be a sign that you have become dependent or addicted.***
***– You need to take the medicine for longer than advised by your doctor***
***– You need to take more than the recommended dose***
***– You are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'***
***– You have made repeated, unsuccessful attempts to quit or control the use of the medicine***
***– When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again ('withdrawal effects')***

***If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely (See section 3, If you stop taking {product name}).***

What you need to know before you take [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.***

**Other medicines and [product name]**

Tell your doctor if you are taking any of the following medicines:

……..

***Cannabidiol (a medicine used to treat seizures)***

***Gabapentin and pregabalin (medicines used to treat epilepsy, nerve pain or anxiety), can increase the risk of opioid overdose, respiratory depression (breathing difficulties) and may be life-threatening.***

Section 3. How to take [product name]

*<Always <take> <use> this medicine exactly as your doctor <or pharmacist> has told you. Check with your <doctor> <or> <pharmacist> if you are not sure.>*

*(The following sentence is applicable where levomethadone has an authorised indication for treatment of pain)*

***Before starting treatment and regularly during treatment, your doctor will discuss with you what you may expect from using {product name}, when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also if you stop taking {product name}).***

*...*

*If you take more than you should*

*If you take too much levomethadone you can experience the following:*

*...*

*…*

***– A brain disorder (known as toxic leukoencephalopathy)***

Section 4. Possible side effects

*Frequency not known:* **(unless other frequency already stated)***:*

***You can become dependent on (product name) (for more information see section 2 Warnings and Precautions)***

***Sleep apnoea (breathing pauses during sleep)***

Section 5. How to store [product name]

*Keep this medicine out of the sight and reach of children.* ***Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been prescribed for them.***

## Annex III

## Timetable for the implementation of this position

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|---|---|
| Adoption of CMDh position: | January 2023 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 12 March 2023 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 11 May 2023 |