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:

Opioid toxicity in infants exposed via breast milk

Based on the PRAC recommendation published in March 2019, the innovators for levomethadone and methadone were requested to provide a critical analysis regarding the risk of infants exposed via breast milk. Not enough evidence for ADRs in infants exposed via breast milk to the company product levomethadone can be retrieved from the three cases related to levomethadone. In contrast, evidence comes from published cases in the literature referring to methadone.

However, as outlined in the parallel assessment for PSUSA/00002004/201905, the published data contains cases of serious adverse events reported in infants exposed to methadone through breastmilk. The overall number of reported cases of toxicity and specifically fatalities in breastfed infants remains extremely low and establishing causality is hugely challenging due to a number of other confounding or pre-disposing factors. The cases presented are considered insufficient to support any update to the PI in this regard. Nevertheless, risk minimisation advice for mothers in relation to monitoring for adverse events in breastfed infants is not routinely present in the PI with only some products highlighting the need to monitor for sedation. Despite the limitations of the available data it is considered prudent to update methadone (a racemic mixture of levomethadone and dextromethadone) PI on use during lactation.

Since it was shown that levomethadone can also pass into breast milk, an amendment to the PI for levomethadone is also recommended.

Interaction with serotonergic drugs

During the PSUR covering period, the FDA published a safety announcement regarding serotonin syndrome for the entire class of opioid pain medicines. A number of MAHs have updated their PI based on the FDA communication. Cases of methadone and serotonin syndrome were identified in EVDAS, all reporting concomitant medication(s), such as SSRIs, SNRIs, TCA, or illicit substances. An increased body of published literature describing serotonin syndrome in methadone users has also been noted and the role of methadone in these cases cannot be ruled out. In addition, synthetic piperidine opioids (such as methadone) are weak serotonin reuptake inhibitors which could lead to an increase in serotonin levels. Based on these data, the PRAC agreed that, as methadone is a racemic mixture of levomethadone and dextromethadone, updates to section 4.5 of levomethadone SmPC and PIL are also recommended.

Adrenal Insufficiency

During the PSUR covering period, the FDA published a safety announcement regarding adrenal insufficiency for the entire class of opioid pain medicines. A number of methadone MAHs have updated their PI based on the FDA communication. The majority of SmPCs have a warning on the risk of worsening of adrenal insufficiency in subjects with pre-existing adrenocortical insufficiency. In EVDAS there are 8 cases (2 spontaneous and 6 from literature) highlighting adrenal insufficiency associated with methadone use.

The evidence from individual case safety reports and published literature is limited, but a number of plausible mechanisms for methadone-induced adrenal insufficiency have been published in the medical literature to support that opioid administration may interact with hypothalamic-pituitary pathways and

be associated with a decreased glucocorticoid response to acute activation of the HPA axis. ACTH-mediated cortisol release was significantly lower in chronic methadone users, suggesting that chronic opiate use may deplete the ACTH/betaendorphin system, thus producing secondary hypoadrenalism; 5 addicted patients treated with methadone showed a decrease of cortisol release after ACTH. Similar to the approach taken with morphine, and due to the seriousness of the potential risk, the PRAC agreed that, as methadone is a racemic mixture of levomethadone and dextromethadone, updates to section 4.4 of levomethadone SmPC (and to the PIL), in order to introduce a warning that opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy, are recommended.

Decreased Sex Hormones

During the PSUR covering period, the FDA published a safety announcement regarding decreased sex hormones for the entire class of opioid pain medicines. A number of MAHs have updated their PI based on the FDA communication. Opioids, both endogenous and exogenous, can bind to opioid receptors primarily in the hypothalamus, and potentially also in the pituitary and the gonads, to modulate gonadal function. Data suggests that most opioids, when used for a long-term, are capable of inducing hypogonadism with or without symptoms of sexual dysfunction. Data from spontaneous reports is more difficult to interpret given the nature of the reporting and expected confounding factors. Common manifestations include low libido, erectile dysfunction and amenorrhea which are labelled in section 4.8 of most reviewed SmPCs. The plausible mechanism of action, already listed PTs and relevant literature publications, provide sufficient justification to recommend an update to section 4.4 of the SmPC of methadone containing products. Such updates are therefore also recommended by PRAC for levomethadone.

Hypoglycaemia

A number of scientific articles were published during the reporting interval under review highlighting serious cases of hypoglycaemia in the context of methadone overdose or dose escalation, with some showing a strong association between methadone exposure and reduction in blood glucose, and a significantly increased rate of hypoglycaemia. The effect appears to be comparable for both IV and oral administration of methadone. A clear dose-response curve is evident and similar effects have not been seen for other opioids, suggesting that this effect may be specific to methadone. Methadone's relatively long half-life in comparison to other opioids may suggest a mechanism related to its constant effect on the HPA axis, although additional investigation is required. Given the large number of publications during the reporting interval, all highlighting serious cases of hypoglycaemia in the context of methadone overdose or dose escalation it is recommended to update section 4.4, 4.8 and 4.9 of the SmPC (and corresponding updates to the PIL) with the PT hypoglycaemia. Such updates are therefore also recommended by PRAC for levomethadone.

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~~)

1. Opioid toxicity in infants exposed via breast milk

Summary of Product Characteristics

Section 4.6 Lactation

Levomethadone is excreted in breast milk at low levels.

For levomethadone the decision to recommend breast-feeding should take into account clinical specialist advice and consideration should be given to whether the woman is on a stable maintenance dose of levomethadone and any continued use of illicit substances. If breastfeeding is considered, the dose of levomethadone should be as low as possible. Prescribers should advise breastfeeding women to monitor the infant for sedation and breathing difficulties and to seek immediate medical care if this occurs. Although the amount of levomethadone excreted in breast milk is not sufficient to fully suppress withdrawal symptoms in breast-fed infants, it may attenuate the severity of neonatal abstinence syndrome. If it is necessary to discontinue breastfeeding it should be done gradually, as abrupt weaning could increase withdrawal symptoms in the infant.

Package leaflet:

Section 2

Pregnancy and Breast-feeding

Talk to your doctor if you are breastfeeding or thinking of breast-feeding while you are <taking><treated with>levomethadone as it may affect your baby. Monitor your baby for abnormal signs and symptoms such as increased drowsiness (more than usual), breathing difficulties or limpness. Consult your doctor immediately if you notice any of these symptoms.

2. Adrenal Insufficiency

Summary of Product Characteristics

Section 4.4

Adrenal insufficiency
Opioids may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Package Leaflet

Section 2 Warnings and precautions

Talk to your doctor or pharmacist if you experience any of the following symptoms while taking X:
- **Weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of the adrenals producing too little of the hormone cortisol, and you may need to take hormone supplement.**

3. Decreased Sex Hormones

Summary of Product Characteristics

Section 4.4

Decreased Sex Hormones and increased prolactin

Long-term use of opioids may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Package Leaflet

Section 2 Warnings and precautions

Long-term use of opioids may cause decreased sex hormone levels and increased levels of the hormone prolactin. Contact your doctor if you experience symptoms such as decreased libido, impotence or absence of menstruation (amenorrhea).

4. Interaction with serotonergic drugs

Summary of Product Characteristics

Section 4.5

Serotonergic drugs:

Serotonergic syndrome may occur with concomitant administration of methadone (a racemic mixture of levomethadone and dextromethadone) with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

Package Leaflet

Section 2 – Other medicines and levomethadone

The risk of side effects increases, if you use levomethadone concomitantly with antidepressants (such as citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, amitriptyline, clomipramine, imipramine, nortriptyline). Contact your doctor if you experience symptoms such as:

- **Mental-status changes (e.g. agitation, hallucinations, coma)**
- **Fast heartbeat, unstable blood pressure, fever**
- **Exaggeration of reflexes, impaired coordination, muscle stiffness**
- **Gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea)**

5. Hypoglycaemia

Summary of Product Characteristics

Section 4.4

Hypoglycaemia

Hypoglycaemia has been observed in the context of methadone (a racemic mixture of levomethadone and dextromethadone) overdose or dose escalation. Regular monitoring of blood sugar is recommended during dose escalation (see section 4.8 and section 4.9)

Section 4.8

Metabolism and nutrition disorders SOC

Hypoglycaemia (frequency not known).

Section 4.9

Hypoglycaemia has been reported.

Package Leaflet

Section 3 - If you take more levomethadone than you should
It can result in **low blood sugar**

Section 4 - Possible Side effects

Frequency not known: **low blood sugar**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January /2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	15 March 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	14 May 2020