VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Opiate dependence

Both individual and environmental factors, influence whether a person who experiments with opioid drugs will continue taking them long enough to become dependent or addicted. Addiction requires, in addition to regular heavy use, four symptoms: tendency to increase dosage, an overwhelming desire or need to continue use and to obtain the drug by any means and a detrimental effect on the individual and society.

There were 15.5 million opioid-dependent people globally in 2010 (0.22%). Prevalence was higher among males than females, and peaked between the ages of 25 to 29 years. Prevalence was higher than the global pooled prevalence in Australasia (0.46%), western Europe (0.35%) and North America (0.30%). Opioid dependence was estimated to account for 9.2 million disability-adjusted life years (DALYs) globally (0.37% of global DALYs) in 2010, a 73% increase on DALYs estimated in 1990.

This burden is estimated to have increased markedly over time, with increased prevalence of dependence the predominant driver of increased burden, rather than changes in the age structure or size of the global population.

Severe chronic pain

The International Association for the Study of Pain defines it as *"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*. Chronic pain is usually defined as pain lasting more than 3 months and almost certainly has some, albeit variable, element of central sensitization. Chronic pain is a complex sensory and emotional experience that varies widely between people depending on the context and meaning of the pain and the psychological state of the person.

There are currently many differences in estimates of the prevalence of chronic pain in Europe, which typically range between 10–30% of the adult population, but studies have reported prevalence as high as 50% or as low as 2%.

It is estimated that approximately one in five of the adult population in Europe suffers chronic pain, which is therefore more prevalent than asthma or diabetes.

Strategies for treatment of chronic pain include antidepressants that increase synaptic norepinephrine and serotonin, agents that reduce neuronal excitability, analgesics and opioids.

VI.2.2 Summary of treatment benefits

Methadone is a synthetic, long acting opioid with pharmacological actions qualitatively like morphine and is active by oral and parenteral routes of administration.

Controlled trials show that the use of methadone tapers in patients who misuse other opioids is superior to placebo and α2-adrenergic agonist-based regimens for managing withdrawal symptoms and retaining patients in treatment programs.

Methadone treatment reduces relapse rates, facilitates behavioral therapy, and enables patients to concentrate on life tasks such as maintaining relationships and holding a job.

Methadone is also a good therapeutic alternative to morphine sulfate and other opiate analgesics in the treatment of severe chronic pain.

It is well absorbed orally, has analgesic effects comparable to other μ-opiate receptor analgesics, like morphine, has a long half-life, and is not metabolized to any active metabolites that may pose a risk to the patient. Parenteral methadone is about twice as potent as oral methadone.

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns relating to treatment benefits that the MAH is aware of.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Disorder in the heart (QT interval prolongation (including Torsade de Pointes))	Cases of QT-interval prolongation and torsade de pointes have been reported during treatment with methadone, especially at high doses.	Methadone must be administered with caution to patients at risk to develop prolonged QT. All patients should be monitored with EKG before

Risk	What is known	Preventability
		initiation of analgesic therapy as well as at steady state if other concurrent risk factors for QT-prolongation exist and in elderly patients when dosing of methadone exceeds 50 mg/day. EKG should also be monitored in all patients before initiation of therapy and at steady state before dose increase of methadone exceeding 100 mg/day.
Use in patients with kidney and liver problems (Use in patients with renal or hepatic impairment)	The metabolism of methadone may be reduced at impaired hepatic function, as opioids are metabolized in the liver. The medicinal product may also cause urine retention.	Patients with impaired renal-or hepatic function should take methadone with caution, and a dose adjustment may be required. A lower initial dose must be administrated in patients with hypothyroidism, myxoedema (severe hypothyroidism), renal impairment, hepatic impairment, asthma or decreased lung volume, and urethral stricture or prostatic hypertrophy.
Intoxication in children	Children are more sensitive than adults, which is the reason why poisoning may occur at very low doses.	Children must not take methadone. To avoid that children by mistake take methadone when it is used at home, it should be stored in a safe place, kept out of reach of children.
Drug interaction with a class of antidepressants (Interaction with MAO inhibitors)	Concurrent administration of MAO-inhibitors may result in reinforced central nervous system inhibition, severe hypotension and/or apnoea.	Patients must not take methadone in combination with MAO-inhibitors or within two weeks after such administration.
Interaction with drugs that are used by the enzyme CYP3A4, responsible for the oxidation of foreign organic molecules (Interaction with CYP3A4 inducers or inhibitors)	Methadone is a substrate for CYP3A4. Induction of CYP3A4 increases the elimination of methadone and leads to decreased plasma levels. The consequences of the enzyme induction are more pronounced if the inducer is administrated after the	Patients with using CYP3A4 inducers or inhibitors should use methadone with caution.

Risk	What is known	Preventability
	treatment with methadone has been initiated. Abstinence symptoms have been reported as a consequence of such interactions and it may therefore be necessary to increase the methadone dose. Inhibition of CYP3A4 decreases the elimination of methadone. Concurrent administration of CYP3A4-inhibitor may increase plasma concentrations of methadone.	
Reduced urge to breathe (Respiratory depression)	The most serious undesirable effect is respiratory depression, which may occur in the stabilization phase. Pulmonary oedema, respiratory depression are uncommon adverse reactions.	Patients with respiratory depression must not take methadone. Acute asthma attacks, severe obstructive pulmonary disease, cor pulmonale, impaired respiratory reserve, hypoxia and hypercapnia are relative contraindications.

Important potential risks

Risk	What is known
Use in pregnancy and breastfeeding	Limited data on the use of methadone during pregnancy in humans show no increased risk of congenital malformation. Withdrawal symptom/respiratory depression may occur in neonates of mothers that were treated with methadone chronically during the pregnancy. A QT prolonging effect following maternal methadone exposure cannot be excluded, and a 12-lead electrocardiogram should be performed if the neonate has bradycardia, tachycardia or an irregular heart rate. Animal studies have shown reproductive toxic effects. Use of methadone immediately before and after delivery is not recommended due to the risk of neonatal respiratory depression. Methadone is excreted in breast milk and the average milk/plasma quote is 0.8. Breastfeeding may be performed at doses up to 20 mg daily. At higher doses the benefits of breastfeeding must be weighed towards the possible negative effects of the child.

Missing information

Risk	What is known
Use in children	Children are more sensitive than adults, which is the reason why poisoning may occur at very low doses. Methadone must not be given to children. No data regarding the use in children are available.

VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Metadon 2care4 5, 10, 20 & 40 mg tablets can be found in the Metadon 2care4 5, 10, 20 & 40 mg tablets national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

VI.2.7 Summary of changes to the Risk Management Plan over time

This section is not applicable as this is version 01 of RMP.