VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Levomethadone is indicated as substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care. Opioid users entering specialist treatment are on average 33 years old, with female patients being younger in most countries. Across Europe, male opioid clients outnumber their female counterparts by a ratio of about three to one. The great majority of opioid clients report having started to use the drug before the age of 30, with almost half (46 %) of all opioid clients having done so before the age of 20. In general, opioid users report higher levels of homelessness and unemployment and lower levels of education than primary users of other drugs, and they are usually concentrated in urban areas. Source: EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) 2012 Annual report on the state of the drugs problem in Europe
http://www.emcdda.europa.eu/publications/annual-report/2012

VI.2.2 Summary of treatment benefits

Levomethadone reduces withdrawal symptoms in people addicted to heroin or other narcotic drugs without causing the "high" associated with the drug addiction. Levomethadone treatment is an integral part of detoxification and maintenance programs in case of opioid addiction.

There are several relevant objectives of levomethadone maintenance therapy:

- to suppress signs and symptoms of opioid withdrawal,
- to extinguish opioid-drug craving, and
- to block the reinforcing effects of illicit opioids.

Each of these objectives is accomplished in phases, rather than at once, relying on the administration of adequate levomethadone doses to achieve and sustain optimum blood levels. Although overdoses can be harmful, insufficient levomethadone treatment is largely ineffective and thus, needs to be avoided.

Efficacy of levomethadone in the claimed indication has been proven by its use in this indication for over 10 years and is thus, well established in medical practice. As a full opioid agonist, levomethadone is associated with the entire spectrum of opioid effects. When properly prescribed and used, levomethadone is an effective and safe medication with an established safety profile. Published information confirms a comparable safety profile of levomethadone and methadone. However, it appears that levomethadone confers advantages regarding cardiac safety and side effects for sp ecial patient groups due to the absence of *d*-methadone.

VI.2.3 Unknowns relating to treatment benefits

In elderly patients and in patients with renal disorders, severe chronic hepatic disorders or a bad general condition there is a risk of increased exposure to levomethadone, and dose reduction is recommended in these patients.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Respiratory depression	Levomethadone is known to cause reduced breathing which can result in serious	Respiratory depression can be avoided by carefully

Risk	What is known	Preventability
	respiratory depression with associated shock and cardiac arrest.	controlling the dosage of the Levopidon treatment and by early recognition.
Heart disease	Levomethadone is known to cause side effects to the heart in higher doses. Since the risk for very serious side effects to the heart are dose related the daily dose of levomethadone should not exceed 100 mg/day. Treatment with higher doses should be restricted to medical professionals with extensive experience in Levopidon treatment.	Heart conditions can be avoided by carefully controlling the dosage of the Levopidon treatment and by early recognition.
Use of Levopidon in patients with liver impairment	Patients suffering from conditions in the liver that weaken the livers ability to metabolise levomethadone are at risk of exposure to higher plasma levels of levomethadone.	Patients need to inform their medical physicians of any know condition related to reduced liver function. Furthermore, medical practitioners need to take into account the patient's ability to metabolize levomethadone and adjust the dose accordingly.
Use of Levopidon in patients with kidney impairment	Patients suffering from conditions in the kidneys that weaken the kidneys ability to excrete levomethadone are at risk of exposure to higher plasma levels of levomethadone.	Patients need to inform their medical physicians of any know condition related to reduced kidney function. Furthermore, medical practitioners need to take into account the patient's ability to excrete levomethadone and adjust the dose accordingly.
Drug interactions	Levomethadone acts with or against, a number of other substances that can reduce or enhance levomethadone's effectiveness or other medicines that are taken simultaneously while on Levopidon treatment. These include MAO inhibitors, other narcotic substances, substances that affect liver metabolism (CYP3A4 inducers or inhibitors, CYP2D6 inhibitors) or other nervous system depressive products.	Patients need to inform their medical physicians of any medication or substances that they are currently taking and a corrective dose or action can be taken. Furthermore, medical practitioners need to take into account the patient's medical history and current medications and adjust the dose accordingly.
Use in pregnancy and lactation	There is limited data on the use of levomethadone during pregnancy in humans. What is available shows no increased risk of congenital malformation. Withdrawal symptom/respiratory depression may occur in neonates of	Patients are warned about the known adverse reaction in the reference safety information. Patients are instructed in the reference safety information to talk to their doctor before

Risk	What is known	Preventability
	mothers that were treated with Levopidon chronically during the pregnancy. Arrhythmias of the heart (QT prolonging effect) following maternal levomethadone exposure cannot be excluded, and a 12-lead electrocardiogram should be performed if the neonate has slow, rapid or irregular heart rate. Animal studies have shown reproductive toxic effects with possible malformation in the embryo. In general it is recommended not to detoxify the patient, especially not after the 20th week of pregnancy, instead maintenance treatment with Levopidon is recommended. Use of levomethadone immediately before and after delivery is not recommended due to the risk of neonatal respiratory depression. Lactation: Levopidon may affect the foetus and the nursing baby. Talk to your doctor before taking Levopidon if you are pregnant, think you may be pregnant or are planning to have a baby or you are breast-feeding	taking Levopidon if they are pregnant, think they may be pregnant or plan to become pregnant. The patient is advised to not breast-feed while using Levopidon.

Important potential risks

Risk	What is known
Medication errors; a risk for mixup between methadone and levomethadone products	Levomethadone is approximately twice as potent as the methadone racemate. A potential risk has been identified for mixup between methadone racemate and levomethadone products, which may cause dangerous and fatal intoxications.
Misuse	Levomethadone may increase the risk of opioid addiction, abuse, or misuse. Abuse or misuse by crushing, chewing, snorting, or injection of product may result in fatal overdose
Overdose	Levomethadone use may result in intentional or unintentional overdose. Factors increasing overdose risk include co-occurring use of sedatives or alcohol, use of illicit opioids, of widely varying and often unknown potency, prolonged abstinence - achieved via antagonist treatment or by other means, prolonged abstinence increases the risk of overdose from relapse by lowering the patient's tolerance to opioids. A dose that would

Risk	What is known
	have had minimal effects on the patient when dependent can cause overdose in the abstinent patient. Additional factors associated with overdose are previous overdose, recent inpatient stay for medically supervised withdrawal, and incarceration.

Missing information
None

VI.2.5 Summary of additional risk minimisation 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.

After MA approval, the Summary of Product Characteristics and the Package leaflet for Levopidon can also be found in the local medicines agency authority's website.

This medicine has additional risk minimisation measures to minimise the potential risk of medication errors, misuse and overdose. These are warning on the label of risk of overdose, and the educational material provided in annex 11. The objectives of the additional risk minimisation measures are to address the safety concern of accidental overdose including potentially fatal drug-related overdose, particularly in the setting of illicit diversion. The purpose of the educational material is to inform the healthcare professionals prescribing or administering Levopidon to the patients of these risks and how to minimise them.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Version 1.0 was submitted during application and assessed by the RMS/CMS.

The RMP version 2.0 was submitted as a response with the following updates:

- Use in pregnancy and lactation moved from potential risk to important identified risk
- Medication error, misuse and overdose added as potential risks.
- Educational material proposed to inform about the risk of Medication error, misuse and overdose

The RMP version 3.0 was submitted as response to day 70 and 100 comments and included the following updates:

- Lowest concentration (0.5 mg/ml) removed
- Maximum amount of levomethadone per bottle reduced from 100 mg to 75 mg by removing the largest bottle sizes in the more concentrated solution
- Product name updated to state total amount of levomethadone in mg per bottle

The RMP version 4.0 was submitted to day 120 and 145 comments and included the following updates:

- Amount of levomethadone presented both as mg per bottle and concentration of solution
- Changed DHPC to educational material
- Added follow-up questionnaire for ICSRs reporting overdose

The RMP version 5.0 was submitted to day 205 comments and included the following updates:

- Monitoring program to evaluate effectiveness of the additional risk minimisation
- Minor restructuring of text