VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Opioid addiction is a global problem that affect millions of people worldwide. In 1962 a study performed by Dole and Nyswander[1] proposed methadone for use as maintenance treatment for persons suffering from opioid addiction. Since then methadone maintenance treatment is the most effective treatment of choice for the treatment of chronic heroin addiction.

Around 1960 raw opium and later morphine base for iv injection was introduced into the Swedish illegal market. In 1967 a case-finding study identified 200 opioid addicts. Heroin was introduced in the Swedish illegal market in 1974. Before that time, opioid addiction occurred in a minority of persons working in hospitals or pharmacies as well as a few reported iatrogenic cases of over-prescription. In 1979 the prevalence of hard-core drug users in Sweden was 15,000 and in 1998 the number was raised to 26,000. Female addicts accounted for 25% of these estimates[2].

Before 1960 no specialised treatment for drug addiction existed outside psychiatric hospitals. In 1966 a Swedish national methadone maintenance program was opened at the psychiatric research centre in Ulleråker hospital in Uppsala[2].

VI.2.2 Summary of treatment benefits

Methadone is a narcotic pain reliever in the same category as morphine. The substance chemically binds to the opiate receptors in the brain, bone marrow and the nervous system similar to morphine and other opiates. Methadone acts in a similar way as morphine, but has less sedative effect. Use of methadone can reduce or eliminate the effects of other opiates. Methadone does not create euphoria. By carefully gradually adjusting the dose of methadone until optimal results, this replacement treatment can give a state of "normalcy" for 24-32 hours, followed by progressive withdrawal symptoms, unless a new dose is administered. Properly dosed methadone patients can control withdrawal syndrome and reduce or stop altogether the use of heroin, morphine and similar drugs. When used correctly, methadone maintenance has been found to be medically safe and non-sedating.

Similarly if methadone is used to manage sever pain treatment, the methadone must be tailored to the individual patient's need for pain relief. To quickly achieve full pain relief methadone can initially be dosed with shorter doses in short intervals for a limited time.
There are no significant differences in the treatment benefits between men and women.

VI.2.3 Unknowns relating to treatment benefits

In older patients above 65 years and in patients with renal or hepatic impairment there is a risk of increased exposure to methadone, and caution is recommended in these patients.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Respiratory depression	Methadone is known to cause reduced breathing which can result in serious respiratory depression with associated	Respiratory depression can be avoided by carefully controlling the dosage of the methadone treatment and by

Risk	What is known	Preventability
	shock and cardiac arrest.	early recognition.
Heart disease	Methadone 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 methadone should not exceed 100 mg/day. Treatment with higher doses should be restricted to medical professionals with extensive experience in methadone treatment.	Heart conditions can be avoided by carefully controlling the dosage of the methadone treatment and by early recognition.
Liver impairment	Patients suffering from conditions in the liver that weaken the livers ability to metabolise methadone are at risk of exposure to higher plasma levels of methadone.	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 methadone and adjust the dose accordingly.
Kidney impairment	Patients suffering from conditions in the kidneys that weaken the kidneys ability to excrete methadone are at risk of exposure to higher plasma levels of methadone.	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 methadone and adjust the dose accordingly.
Drug interactions	Methadone acts with or against, a number of other substances that can reduce or enhance methadone's effectiveness or other medicines that are taken simultaneously while on methadone 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.

Important potential risks

Risk	What is known
Use in pregnancy and lactation	There is limited data on the use of methadone during pregnancy in humans. What is available shows 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. Arrhythmias of the heart (QT prolonging effect) following maternal methadone 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 methadone is recommended. Use of methadone immediately before and after delivery is not recommended due to the risk of neonatal respiratory depression. Lactation: Methadone is excreted in breast milk. Breast feeding may be performed at doses up to 20 mg daily. At higher doses the benefits of breast feeding must be weighed towards the possible negative effects towards the child.

Important missing information
None

VI.2.5 Summary of additional risk minimisation measures by safety concern
Routine pharmacovigilance activities are applied.

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
Not applicable.