VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Severe pain
Pain often accompanies chronic illness. A large survey performed in 15 European countries has found that 19% of the population suffers from chronic pain, one third of cases complaining of severe pain. In ca. 5% of these cases, mild painkillers are not sufficient for the control of the patients' pain, and opioid analgesics need to be used for this purpose.

Opioid dependence
The abuse potential of opioid drugs such as heroin and morphine is very high. It is estimated that about 32.4 million adults in the world use opioids illegally including nearly 18 million people (5.9% of the population) in the United States. Substantial regional differences in abuse patterns exist. A mental health survey performed in 2002 in The Netherlands, has found that 11.5% of men and 1.8% of women suffered from some substance use disorder. The disorder is more common in adult males with parental psychiatric history, living without a partner in urban environments, and is often associated with other psychiatric disorders.

VI.2.2 Summary of treatment benefits

Methadone is an opioid pain reliever in the same category as morphine and binds to the same opiate receptors throughout the body. As methadone acts similarly to morphine but has less sedative effect, it can be used to reduce or eliminate the effects of other opiates. By gradually adjusting the dose of methadone until optimal results are achieved, properly dosed methadone patients can control their withdrawal syndrome and reduce or stop their use of heroin, morphine and other similar drugs. When used correctly, methadone maintenance has been found to be medically safe and non-sedating.

Methadone has also been shown to be useful in managing severe pain. Similar to other opioid drugs, the dose of methadone must be adjusted carefully to the individual patient's need for pain relief. There are no significant differences in the treatment benefits between men and women.

VI.2.3 Unknowns relating to treatment benefits

None.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Depressed breathing (respiratory depression)	Methadone may cause breathing difficulties. This is more likely to occur when the drug is given at high doses or is taken together with alcohol or other medicines acting on the central nervous system.	Patients with asthma or respiratory diseases leading to depressed breathing should not take methadone. Methadone should not be taken by patients with delirium caused by chronic alcohol intoxication (delirium tremens). Concomitant intake of methadone with alcohol and other medicines depressing the central nervous system should be avoided.
Heart rhythm disturbances (prolongation of QT interval and *torsades de pointes*)	QT-syndrome is a disorder of the heart's electrical system, recordable as an anomaly on ECG. Methadone has the potential to cause this kind of rhythm disturbance, especially when given at higher doses, in patients with cardiac disorders, or when combined with other medicines, baring the same risk. Often this disorder, either pre-existing or installed after start of methadone therapy is not recognized by patients.	Methadone should not be taken by patients with heart failure. Caution by the treating physician is required when prescribing methadone to patients at risk to heart rhythm disturbances, or taking medicines bearing such risks.
Inability to urinate (urinary retention)	Like other opioids, methadone may diminish the capacity of smooth muscles to contract. This often affects the capacity of passing urine (resulting in retention of urine).	Monitoring for early symptoms. Corrective treatment may be helpful. In serious cases, therapy may have to be altered by the treating physician.
Decreased motility of the digestive tract (reduced GIT motility)	Like other opioids, methadone may diminish the capacity of smooth muscles to contract. This often affects the digestive system, resulting in constipation.	Monitoring for early symptoms. Corrective treatment may be helpful. In serious cases, therapy may have to be altered by the treating physician.
Concomitant use with other medicines (drug-drug interactions)	When methadone is given concomitantly with drugs acting on the central nervous system such as barbiturates	Caution is required from the treating physician when co-prescribing these medicines with methadone.

Risk	What is known	Preventability
	(preventing seizures) and strong sedatives, the effects and side effects might be mutually potentiated. Drugs like naloxone (opioid antidote) and nalbuphine (pain killer) have effects opposite, and may cause acute withdrawal syndrome in patients taking methadone. Phenytoin (preventing seizures and heart rhythm disorders), rifampicin (for treatment of tuberculosis and leprosy) and St. John's wort (herbal remedy for depression) increase the decomposition of methadone. The following medicines increase the risk of heart beat disturbances (QT prolongation and *torsades de pointes*): • drugs themselves used to treat heartbeat disturbances (arrhythmics); • drugs used to treat psychosis (severe mental illness); • several antibiotics (used to treat bacterial infections); • drugs used to treat depression; drugs used to treat allergic reactions (antihistamines).	Caution is required from the treating physician when co-prescribing these medicines with methadone. Caution is required from the treating physician when co-prescribing these medicines with methadone. Concomitant intake of methadone with these medicines should be avoided.
Concomitant use with other medicines may aggravate depression of the activity of the central nervous system (exacerbation of cerebral nervous system depression with CNS depressants and MAO-inhibitors)	When methadone is given concomitantly with drugs depressing the central nervous system and drugs used for treatment of Parkinson's disease and depression (MAO-inhibitors) it may aggravate the depression of the activity of the central nervous system.	Caution is required from the treating physician when co-prescribing MAO-inhibitors with methadone, and 14 days after discontinued treatment with MAO-inhibitors.
Dependence and abuse	Like with other opioids, drug dependence occurs with	Monitoring for early symptoms. If cravings to methadone develop,

Risk	What is known	Preventability
	methadone.	a doctor or pharmacist should be advised. Therapy may have to be altered.
Drug withdrawal	Sudden cessation of the methadone treatment may cause withdrawal symptoms such as sleeplessness, nasal discharge, loss of appetite, diarrhea and pain.	The treatment with methadone should only be paused or stopped in agreement with the doctor.

Important potential risks

Risk	What is known
Toxicity in children	Children are more susceptible to intoxication than adults therefore intoxication can occur even at very low doses.
Use during pregnancy and breast-feeding	There is limited data on the use of methadone during pregnancy in humans. What is available shows no increased risk of congenital malformation. Prenatal exposure to methadone is associated with a neonatal abstinence syndrome (NAS) characterized by central nervous system hyperirritability and autonomic nervous system dysfunction, which often requires medication and extended hospitalization. Use of methadone immediately before delivery is not recommended due to the risk of neonatal respiratory depression. If the mothers are in the methadone programme the neonates are in better condition than if the mothers are abusing illegal drugs. 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.

VI.2.5 Summary of 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.

The Summary of Product Characteristics and the Package leaflet for Marlodon can be found at the homepage of the National Health Authority.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

None.

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

Not applicable as this is the initial risk management plan.