

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Severe pain:

Pain is a global health problem, it is estimated that 10% of the population is somehow affected by severe pain. It affects people of all ages and backgrounds, and the underlying cause of the pain can include severe or chronic diseases such as cancer, and patients may also experience severe or intolerable pain after a surgery or trauma. Risk factors associated with the occurrence of severe pain include other co-morbidities, mental health, disabilities, poor health status, employment and occupational factors.

VI.2.2 Summary of treatment benefits

Severe pain:

Severe pain is often affecting the quality of life of patients and sometimes can be unbearable. Morphine has a strong analgesic effect, acting centrally in the brain and is commonly used for treating severe pain. It has been used clinically to treat severe pain for over a century and has extensive clinical experience.

VI.2.3 Unknowns relating to treatment benefits

Morphine has been used for over a century for treating severe pain, and has extensive clinical experience, therefore there are no unknowns relating to treatment benefits.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Central Respiratory depression	Morphine inhibits the respiratory center in the brain and can cause inadequate, shallow breathing, particularly in patients with reduced respiratory capacity due to pulmonary disease or use of pharmaceuticals.	Morphine should not be given to patients with severe respiratory problems (respiratory depression, severe bronchial asthma or obstructive pulmonary disease). Also, morphine should be used with extreme caution and at reduced doses in patients with impaired lung capacity. Healthcare professionals are instructed that as there can be considerable variability in both the dosage requirement and the patient response, the dose should be adjusted for the individual based on effect and adverse reactions. Respiratory depression is temporary, and breathing will gradually return to normal as morphine is eliminated from the body.
Tolerance and dependence	If morphine is used for a prolonged period of time, usually for more than 1-2 weeks, tolerance and dependency can occur. Tolerance means, that the initial dose may need to be increased to provide the same pain relieving effect. Dependence means, that in case of sudden withdrawal of morphine, withdrawal symptoms will occur. When morphine treatment should be stopped, the doses should be gradually decreased.	Tolerance and dependence naturally occurs with morphine. Treatment duration and doses should be carefully determined. For prolonged treatment, to avoid dependence, the treating physician may switch to different type of analgesics from time to time.
Interaction with MAO inhibitors	If morphine is given together or within 2 weeks after treatment with MAO inhibitors, the two drugs interact with each other and may cause the potentially serious and life threatening serotonin syndrome.	Morphine should be given with great caution during treatment with MAO inhibitors or within 2 weeks after treatment with MAO inhibitors.
Harm to the unborn child when used during pregnancy (Use in pregnancy)	Morphine crosses the placental barrier and may influence the foetus and newborn baby when used during pregnancy and labor. Neonatal abstinence symptoms such as seizures, irritability, vomiting, and increased mortality have been seen after long-term/frequent	Morphine should not be used during pregnancy, especially not during the third trimester, unless the potential benefits justify the possible risks to the foetus. Morphine must not be used in the second stage of labour and

Risk	What is known	Preventability
	administration to pregnant women. When used during labor, morphine can cause respiratory depression to the newborn.	for premature births.
Excretion into breast milk – there is a risk of harm to the child if you are breastfeeding (Use in lactating women)	Morphine is secreted into mother's milk and may affect the nursing baby.	Morphine must not be used during breast-feeding.
Use in patients where the liver functions is reduced and Use in patients where the kidney functions is reduced (Use in patients with hepatic impairment and use in patient with renal impairment)	The elimination of morphine is slower in patients with hepatic impairment. There is a risk of accumulation of morphine in the body and thus overdose or adverse reactions can occur. There is a risk of accumulation of morphine in the body and thus overdose or adverse reactions can occur. Accumulation of morphine can result in long-term respiratory depression.	Hepatic impairment: Morphine must not be given to patients with acute liver disease. Morphine should be used with caution in patients with hepatic impairment. The starting dose should be reduced and dosing interval may be prolonged. Renal impairment: Caution should be exercised and the dose should be reduced in patients with renal impairment

Important potential risks

Not applicable

Missing information

The world-wide exposure to morphine calculated from sales figures equates to more than 29 500 patients-years of using morphine; actual patient numbers are likely to be greater. As such morphine is considered to have been used in a broad section of the population, including the elderly, and the side effects for morphine are well established. There is no important missing information.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a 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 (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures. Any safety concerns will be monitored via routine pharmacovigilance activities.

VI.2.6 Planned post authorisation development plan

Morphine containing products have been on the market for many decades; therefore, their efficacy and safety profile is well established. There is no planned post authorisation development program.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 2.0	28 Jul 2016	Added new Important identified risk: Use in patient with Hepatic impairment Use in patient with renal impairment Use in pregnancy Use in lactating women Overdose	No additional pharmacovigilance activities or No additional risk minimization activities proposed for new important identified risk.
Version 3.0	11 Nov 2016	No changes in safety concerns	No additional pharmacovigilance activities or No additional risk minimization activities proposed for new important identified risk. The RMP was updated as the SmPC was updated based on RMS comment