PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Morfin Abcur, 10 mg/ml, solution for injection, Morphine sulphate 10 mg/ml solution for injection (Ireland and Malta), Morphine sulphate 30 mg/ml solution for injection, Morphine sulphate 60 mg/ml solution for injection, Morphine sulphate 1 mg/5 ml solution for injection, Rhotard Morphine SR 10 mg Tablets, Morphgesic SR 10 mg Tablets, Rhotard Morphine SR 30 mg Tablets, Morphgesic SR 30 mg Tablets, Rhotard Morphine SR 60 mg Tablets, Morphgesic SR 60 mg Tablets, Rhotard Morphine SR 100 mg Tablets and Morphgesic SR 100 mg Tablets (referred to herein as Morphine)

This is a summary of the risk management plan (RMP) for Morphine. The RMP details important risks of Morphine, how these risks can be minimised, and how more information will be obtained about Morphine's risks and uncertainties (missing information).

Morphine's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Morphine should be used.

Important new concerns or changes to the current ones will be included in updates of Morphine's RMP.

I. The medicine and what it is used for

Morfin Abcur, 10 mg/ml, solution for injection is authorised to relieve severe pain. Morfin Abcur, 10 mg/ml, solution for injection contains morphine hydrochloride as the active substance and it is given by subcutaneous, intramuscular route. In urgent cases, morphine can be given slowly intravenously.

Morphine sulphate 10 mg/ml solution for injection (Ireland and Malta), Morphine sulphate 30 mg/ml solution for injection, Morphine sulphate 60 mg/ml solution for injection are authorised to relieve severe pain. They contain morphine sulphate as the active substance and it is given by subcutaneous, intramuscular or intravenous route.

Morphine sulphate 1 mg/ 5 ml injection is used to relieve moderate to severe pain. It contains morphine sulphate as the active substance and it is given by epidural or intrathecal route.

Rhotard Morphine SR 10 mg Tablets, Morphgesic SR 10 mg Tablets, Rhotard Morphine SR 30 mg Tablets, Morphgesic SR 30 mg Tablets, Rhotard Morphine SR 60 mg Tablets, Morphgesic SR 60 mg Tablets, Rhotard Morphine SR 100 mg Tablets and Morphgesic SR 100 mg Tablets are used for pain relief. They contain morphine sulphate as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Morphine, together with measures to minimise such risks and the proposed studies for learning more about Morphine's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Morphine is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Morphine are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Morphine. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Abnormally slow and shallow breathing (Respiratory depression) • Liver dysfunction (Hepatic impairment) • Drug interactions • Physical and/or psychological need of a medicine to function normally (Drug dependency)
Important potential risks	• Use in pregnant and breast-feeding women (Use in pregnancy and lactation)
Missing information	• None

II.B Summary of important risks

Important identified risks

Abnormally slow and shallow breathing (Respiratory depression)	
Evidence for linking the risk to the medicine	SmPC states that severe and prolonged respiratory depression may occur in patients with kidney dysfunction given morphine; this is attributed to the accumulation of the active metabolite

	morphine-6-glucuronide. The major risk of opioid excess is respiratory depression. Morphine can induce severe respiratory depression, particularly in newborns.
Risk factors and risk groups	• Patients with impaired respiratory function • Patients with moderate or severe kidney dysfunction • Concomitant use with CNS depressants • Neonates or infants born to mothers receiving opioid painkillers during late pregnancy or during labour
Risk minimisation measures	**Routine risk minimisation measures:** <u>Morfin Abcur 10 mg/ml solution for injection, Morphine Sulphate 10 mg/ml solution for injection</u> • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 • PL sections 2, 3, 4 <u>Morphine Sulphate 1 mg/5ml solution for injection</u> • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 • PL sections 2, 4 <u>Morphine Sulphate 30 mg/ml Solution for Injection, Morphine Sulphate 60 mg/ml Solution for Injection, Rhotard Morphine SR 10 mg, 30 mg, 60 mg, 100 mg Tablets, Morphgesic SR 10 mg, 30 mg, 60 mg, 100 mg Tablets</u> • SmPC sections 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 • PL sections 2, 3, 4 **Additional risk minimisation measures:** No risk minimisation measures

Liver dysfunction (Hepatic impairment)	
Evidence for linking the risk to the medicine	SmPC states that morphine may precipitate coma in patients with severe liver dysfunction. Increased liver enzymes has been reported with morphine use.
Risk factors and risk groups	• Patients with liver disease
Risk minimisation measures	**Routine risk minimisation measures:** <u>Morfin Abcur 10 mg/ml solution for injection</u> • SmPC sections 4.2, 4.3, 4.4, 4.8

	• PL sections 2, 3 <u>Morphine Sulphate 1 mg/5ml solution for injection</u> • SmPC sections 4.3, 4.4, 4.8 • PL sections 2, 4 <u>Morphine Sulphate 10 mg/ml solution for injection, Morphine Sulphate 30 mg/ml Solution for Injection, Morphine Sulphate 60 mg/ml Solution for Injection</u> • SmPC sections 4.2, 4.3, 4.4, 4.8 • PL sections 2, 3, 4 <u>Rhotard Morphine SR 10 mg, 30 mg, 60 mg, 100 mg Tablets, Morphgesic SR 10 mg, 30 mg, 60 mg, 100 mg Tablets</u> • SmPC sections 4.3, 4.8 • PL sections 2, 4 **Additional risk minimisation measures:** No risk minimisation measures

Drug interactions	
Evidence for linking the risk to the medicine	SmPC mentions that barbiturates, alcohol enhance the respiratory depressant effect of opiates and opioids. Clomipramine, amitriptyline and nortriptyline enhance the analgesic effect of morphine. MAO inhibitors may enhance the effect of morphine (respiratory depression and low blood pressure). Serotonergic syndrome has been reported with simultaneous use of pethidine and MAO inhibitors. Combined morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine) reduce the analgesic effect by competitive blocking of receptors, thereby increasing the risk of withdrawal symptoms. The depressant effects of morphine may be enhanced, or the effects of other compounds enhanced, by depressants of the CNS such as alcohol, anaesthetics, hypnotics and sedatives, tricyclic antidepressants and phenothiazines, as well as muscle relaxants, gabapentin and antihypertensives. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine sulphate. The action of morphine may in turn affect the activities of other compounds, for example its gastro-intestinal effects may delay absorption as with mexilitine or may be counteractive as with metoclopramide. The analgesic effect of opioids tends to be enhanced by co-administration of dexamfetamin and hydroxyzine.

	Anti-histamines, anti-parkinsonian agents and anti-emetics, may interact with morphine sulphate to potentiate anti-cholinergic adverse events. Plasma concentrations of morphine sulphate may be reduced by rifampicin. Morphine may reduce the efficacy of water pills (diuretics). Propranolol has been reported to enhance the lethality of toxic doses of opioids in animals, although the significance of this finding is not known for man.
Risk factors and risk groups	Simultaneous use of morphine with rifampicin, clomipramine, amitriptyline, nortriptyline, MAO inhibitors, combined morphine agonists/antagonists, CNS depressants, dexamfetamin, hydroxyzine, anti-histamines, anti-parkinsonian agents and anti-emetics, diuretics and propranolol
Risk minimisation measures	**Routine risk minimisation measures:** <u>Morfin Abcur 10 mg/ml solution for injection</u> • SmPC sections 4.4, 4.5 • PL section 2 <u>Morphine Sulphate 1 mg/5ml solution for injection, Morphine Sulphate 30 mg/ml Solution for Injection, Morphine Sulphate 60 mg/ml Solution for Injection</u> • SmPC section 4.5, 6.2 • PL section 2 <u>Morphine Sulphate 10 mg/ml solution for injection, Rhotard Morphine SR 10 mg, 30 mg, 60 mg, 100 mg Tablets, Morphgesic SR 10 mg, 30 mg, 60 mg, 100 mg Tablets</u> • SmPC section 4.5 • PL section 2 **Additional risk minimisation measures:** No risk minimisation measures

Physical and/or psychological need of a medicine to function normally (Drug dependency)	
Evidence for linking the risk to the medicine	Published literature and SmPC state that morphine has addictive properties and tolerance may be developed to morphine effects. Morphine and related analgesics may produce both physical and psychological dependence. Drug dependence may occur after treatment for one or two weeks with therapeutic doses. Some cases of dependence have been observed after only 2 to 3 days.

	Patient may develop tolerance to the drug with long term use and require progressively higher doses to maintain pain control. Prolonged use of this product may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. Morphine sulphate has an abuse profile similar to other strong agonist opioids. Morphine sulphate may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including morphine. Abuse of Rhotard Morphine SR/ Morphgesic SR tablets by parenteral administration can be expected to result in serious adverse events, which may be fatal.
Risk factors and risk groups	• Opioid dependent patients • Patients with a history of alcohol and substance abuse
Risk minimisation measures	**Routine risk minimisation measures:** Morfin Abcur 10 mg/ml solution for injection • SmPC section 5.3 Morphine Sulphate 1 mg/5ml solution for injection, Morphine Sulphate 10 mg/ml solution for injection, Morphine Sulphate 30 mg/ml solution for injection, Morphine Sulphate 60 mg/ml solution for injection • SmPC sections 4.4, 4.8, 4.9 • PL sections 2, 4 Rhotard Morphine SR 10 mg, 30 mg, 60 mg, 100 mg Tablets, Morphgesic SR 10 mg, 30 mg, 60 mg, 100 mg Tablets • SmPC sections 4.4, 4.8, 4.9, 5.1 **Additional risk minimisation measures:** No risk minimisation measures

Important potential risks

Use in pregnant and breast-feeding women (Use in pregnancy and lactation)	
Evidence for linking the risk to the medicine	SmPC mentions that, there are limited amount of data from the use of morphine in pregnant women. Morphine crosses the placenta. Studies in animals have shown reproductive toxicity. Long term use of morphine during pregnancy may result in opioid withdrawal state in baby. Morphine can increase or shorten the

	duration of labour. Morphine can produce abnormally slow and shallow breathing in the newborn, if it is administered during labour. Morphine is excreted into breast milk, where it reaches higher concentrations than in maternal blood. Clinically relevant concentrations of morphine may be reached in nursing infants.
Risk factors and risk groups	• Use in pregnant and breast-feeding women • Men and women of child producing/child bearing potential
Risk minimisation measures	**Routine risk minimisation measures:** Morfin Abcur 10 mg/ml solution for injection • SmPC section 4.6 • PL section 2 Morphine Sulphate 1 mg/5ml solution for injection, Morphine Sulphate 10 mg/ml solution for injection, Morphine Sulphate 30 mg/ml Solution for Injection, Morphine Sulphate 60 mg/ml Solution for Injection • SmPC section 4.6, 5.2 • PL section 2 Rhotard Morphine SR 10 mg, 30 mg, 60 mg, 100 mg Tablets, Morphgesic SR 10 mg, 30 mg, 60 mg, 100 mg Tablets • SmPC section 4.3, 4.6 • PL section 2 **Additional risk minimisation measures:** No risk minimisation measures

Missing Information

None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Morphine.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Morphine.