SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Morfin Abcur, 10 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 10 mg morphine hydrochloride corresponding to 7.6 mg morphine.

5 ml contains 50 mg morphine hydrochloride corresponding to 37.95 mg morphine

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear solution, pH 3-5.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain conditions

4.2 Posology and method of administration

Posology

Administration and dosage should be individualized taking into account the nature and severity of pain and the patient's general condition.

Individual criteria for the dose depend on the patient's age, weight, pain severity, and medical and analgesic history.

Adults: 1 – 1.5 ml solution for injection (10-15 mg morphine hydrochloride) subcutaneously or intramuscularly 1- 3 times daily. In urgent cases, morphine can be given slowly intravenously. Morfin Abcur may also be used in combination with continuous infusions and with patient-controlled analgesic therapy pumps.

Elderly
Caution should be exercised and the dosage initially reduced in morphine treatment of elderly patients.

Hepatic impairment
Caution should be exercised and the dosage initially reduced in morphine treatment in patients with hepatic impairment.

Renal impairment
Caution should be exercised and the dosage initially reduced in morphine treatment in patients with renal impairment.

Treatment control
Nausea, vomiting and constipation can sometimes be counteracted by 0.25-0.5 mg atropine subcutaneously. Morphine alone should not be given in biliary or renal colic attacks, since the cramps then might increase. In these cases, morphine should be given in combination with antispasmodics. Respiratory depression can be reversed by naloxone.

Method of administration
subcutaneously or intramuscularly. In urgent cases, morphine can be given slowly intravenously.

Treatment goals and discontinuation
Before initiating treatment with Morfin Abcur, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with Morfin Abcur, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
Morfin Abcur should not be used longer than necessary.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Secretion stagnation, respiratory depression, acute liver disease, agitation states during affect of alcohol or hypnotics.

4.4 Special warnings and precautions for use

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Severe cutaneous adverse reactions (SCARs)
Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.
If signs and symptoms suggestive of these skin reactions appear, morphine should be withdrawn and an alternative treatment considered.

Hepatobiliary disorders
Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.
Addictive agent. Take extreme caution when prescribing this drug. The dose may need to be reduced in bronchial asthma, upper respiratory tract obstruction, head injuries, hypotension associated with hypovolaemia, hypothyroidism, impaired hepatic and renal function, inflammatory bowel diseases,

pancreatitis, bile duct spasm, urinary tract spasm and in the treatment of elderly patients. Caution should be exercised in patients with prostate hypertrophy, myasthenia gravis.

Morphine should not be used in idiopathic pain or in pain with psychopathological characteristics (related to the lack of pain relief).
Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

Morphine alone should not be administered during biliary or renal colic attacks as it may increase the cramp. In these cases morphine should be given in combination with a spasmolytic.
Following encephalitis, the effects of morphine can be enhanced.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)
Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased Sex Hormones and increased prolactin
Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Morphine has an abuse potential similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol or drug abuse.

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Morfin Abcur.

Repeated use of Morfin Abcur can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment, can increase the risk of developing OUD. Abuse or intentional misuse of Morfin Abcur may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (eg. major depression, anxiety and personality disorders).

Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

Before initiating treatment with Morfin Abcur and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Morfin Abcur and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not

possible. If a decision is made to prescribe Morfin Abcur concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Treatment with MAO inhibitors, see section 4.5.

Oral P2Y12 inhibitor antiplatelet therapy
Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Barbiturates potentiate the respiratory depressant effect of opiates and opioids. The combination should therefore be avoided.

Rifampicin induces the metabolism of orally administered morphine to such an extent, that higher doses than normal are required for analgesic effect.

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

Clomipramine and amitriptyline and nortriptyline enhance the analgesic effect of morphine, probably due to increased bioavailability. Dose adjustment may be required.

MAO inhibitors may potentiate the effect of morphine (respiratory depression and hypotension). Serotonergic syndrome has been reported with concomitant use of pethidine and MAO inhibitors, and can therefore not be excluded in the combination of morphine and MAO inhibitors.

Small amounts of alcohol can dramatically potentiate the weak respiratory depressant effect of morphine. The combination should therefore be avoided.

Combined morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine) reduce the analgesic effect by competitive blocking of receptors, thereby increasing the risk of withdrawal symptoms.

Gabapentin: Attention should be paid to the risk of CNS symptoms in the choice of treatment. If the two products are given concomitantly, consider reducing the gabapentin dose. Patients should therefore be monitored carefully regarding signs of CNS depression such as somnolence, and the gabapentin or morphine dose should be reduced accordingly.

Sedative medicines such as benzodiazepines or related drugs
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including hypnotics, general anaesthetics, phenothiazines, other tranquilisers, muscle

relaxants, antihypertensives, and pregabalin. 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.

4.6 Fertility, pregnancy and lactation

Men and women of childbearing potential
Due to the mutagenic properties of morphine, it should not be administered to men and women of child-producing/child bearing potential unless effective contraception is assured (see section 5.3).

Pregnancy
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 (see section 5.3).
For this reason, morphine must only be used during pregnancy in cases where the maternal benefit clearly outweighs the risk for the child.

Long term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Morphine can prolong or shorten the duration of labour. Morphine can produce respiratory depression in the neonate, if it is administered during labour. Infants born to mothers receiving opioid analgesics during late pregnancy or during labour should be monitored for signs of respiratory depression or withdrawal syndrome, and (if necessary) treated with a specific opioid antagonist. Especially during the 2 to 3 hours before expected partum Morfin Abcur should only be administered on strict indication and following a mother benefit versus baby risk analysis.

Breastfeeding
Morphine is excreted into breast milk, where it reaches higher concentrations than in maternal plasma.
Since clinically relevant concentrations of morphine may be reached in nursing infants, breast-feeding is not recommended (see section 5.2).

Fertility
There are no clinical data on the effects of morphine on male or female fertility.
Animal studies have shown that morphine had adverse effects on animal fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Treatment with Morphine Abcur may impair reaction ability.
This should be considered when alertness is required e.g when driving.

4.8 Undesirable effects

Approximately 20% of the patients experience nausea and vomiting. Most side effects are dose dependent.

Tabulated list of adverse reactions
Adverse reactions reported in clinical trials and in the post-marketing period are included in the table below. The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000) and not known (cannot be estimated from available data).

SOC	Common	Uncommon	Rare	Not known
Immune system disorders				Anaphylactic reaction
Psychiatric disorders		Dysphoria		Agitation Dependence
Nervous system disorders	Sedation*	Dizziness Light headedness		Convulsions Hyperaesthesia Hyperalgesia (see section 4.4)

SOC	Common	Uncommon	Rare	Not known
				Allodynia Paraesthesia Hyperhidrosis
Eye disorders	Miosis			
Cardiac disorders				Palpitations Bradycardia Tachycardia
Vascular disorders			Orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders	Bronchospasm			Respiratory depression**** Central sleep apnoea syndrome
Gastrointestinal disorders	Constipation Nausea** Vomiting**			Narcotic bowel syndrome Dry mouth Pancreatitis
Hepatobiliary disorders		Bile duct spasm		Spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders		Pruritus		Diaphoresis Urticaria Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Urinary retention	Urinary tract spasm***		
General disorders and administration site conditions				Drug withdrawal (abstinence) syndrome
Investigations	Increased ADH release			

*Sedation normally decline after a few days' administration.
**Nausea and vomiting often decline during long-term use.
***Spasm of the biliary and urinary tract may occur in predisposed individuals.
****The respiratory depressant effect is dose dependent and rarely a clinical problem. Habituation and tolerance do not usually cause any problems in the treatment of severe cancer pain.

Drug dependence and withdrawal (abstinence) syndrome
Repeated use of Morfin Abcur can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4). An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued, or opioid antagonists administered or can sometimes be experienced between doses. For management, see 4.4.
Physiological withdrawal symptoms include: Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, “drug craving” is often involved.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in
[To be completed nationally]

4.9 Overdose

Symptoms: Signs of overdose include pin-point pupils, pneumonia aspiration, respiratory depression and hypotension. Circulatory disorders and coma may occur in severe cases. Death may occur from respiratory failure.

Management: If justified gastric lavage, charcoal, laxative when taken orally. Respiratory depression at morphine intoxication can be reversed with naloxone, initially 0.4 mg for adults (children 0.01 mg/kg) slowly intravenously, the dose is gradually increased if necessary.
Continuous infusion of naloxone can sometimes be a practical option.
Respiratory treatment on the indication (with PEEP in pulmonary edema). Naloxone cannot replace respiratory therapy in serious intoxication. Intravenous fluids (electrolyte, glucose), blood gas control, acidosis correction. Symptomatic therapy.

Toxicity: Toxic dose for adults (no onset of tolerance) is usually in the range of 40-60 mg orally (30 mg parenterally). Scopolamine, hypnotics and alcohol potentiate toxic effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids, ATC code: N02AA01

Morphine is an opioid analgesic with strong analgesic effect. The analgesic effect is due to an altered pain perception and partly to an increase in pain threshold. Morphine probably exerts its analgesic effect at different levels within the CNS.

In elderly patients the analgesic effect of morphine is increased. The central nervous system effects of morphine also include respiratory depression, psychiatric symptoms, nausea and vomiting, miosis and release of antidiuretic hormone. The respiratory depressant effect of morphine is due to an inhibition of the stimulatory effect of carbon dioxide on the respiratory center in the medulla. This effect can lead to respiratory insufficiency in patients with reduced ventilation capacity due to lung disease or the effects of other pharmaceuticals. After encephalitis, the effects of morphine can be amplified. Intoxication with morphine requires respiratory supportive therapy and administration of an antidote.

Among psychiatric symptoms are present euphoria, but also depression and sleep, concentration and memory disorders. Due to stimulation of the dopamine receptors in the "trigger zone" of the medulla, nausea and vomiting can occur. The increased release of antidiuretic hormone contributes to decreased urine volumes during morphine treatment. Morphine increases the tone of the smooth muscles in the digestive tract. This leads to constipation by sustained passage of food through the digestive tract. Further the pressure in the biliary and urinary tract increases, why morphine is less suitable in bile duct- or urinary tract spasm. Morphine has addictive properties and tolerance may be developed to morphine effects. However, this usually does not cause any problems in the treatment of severe pain associated with cancer.

M6G, a major metabolite of morphine, has pharmacological actions indistinguishable from those of morphine. During chronic treatment it contributes with a significant part of the analgesic effects of morphine.

5.2 Pharmacokinetic properties

<u>Absorption</u>
Maximum concentration in blood is reached within 10-20 minutes.

<u>Distribution</u>
The volume of distribution is about 3 L/ kg with a plasma protein binding of approximately 35%. The clearance is approx. 24 ml/min * kg and half-life is approximately 2-3 hours.

Biotransformation
Morphine does not have dose-dependent kinetics. The major metabolites, morphine-3-glucuronide (lacks analgesic effect) and morphine-6-glucuronide (more potent than morphine itself). Morphine and its metabolites undergo enterohepatic circulation.

Elimination
The elimination of morphine occurs primarily by glucuronidation and excretion of unchanged morphine in urine is <0.1%.
The bioavailability may be increased by liver cancer.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. There have been no long-term animal studies on the tumorigenic potential of morphine. Effects in non-clinical studies were observed for genotoxicity, and toxicity to reproduction and development.

Mutagenic and tumorigenic potential
There are clearly positive findings available with regards to mutagenicity, which indicate that morphine has a clastogenic effect and that, furthermore, this effect exerts an influence on gametes. Thus, morphine is to be regarded as a mutagenic substance and such an effect may also be assumed in humans.

Reproductive toxicity
Animal studies showed a potential for damage in offspring throughout the entire duration of gestation (CNS malformations, growth retardation, testicular atrophy, changes in neurotransmitter systems and behavioural patterns, dependence). In male rats, reduced fertility and chromosomal damage in gametes have been reported. In addition, morphine had an effect on male sexual behaviour and fertility in various animal species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid *(for pH adjustment)*
Water for injections

6.2 Incompatibilities

Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5- fluorouracil.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Keep the ampoule in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Clear glass ampoules 5 x 1 ml, 10 x 1 ml and 10 x 5 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Splashes on the skin and in the eyes may cause burning, redness and itching. Avoid direct contact with the product.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]
Date of latest renewal: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

17 October 2023