

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sevredol 20 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg Morphine Sulfate.

Also contains 197.5 mg lactose. Film-coating contains small amount (< 1 mg) Sunset yellow (E110).

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Pink, film coated, biconvex, capsule-shaped tablet, marked with a scoreline with "IR" to the left and "20" to the right with a plain reverse side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain.

4.2 Posology and method of administration

Posology

Adults and children over 12 years.

The dosage of **Sevredol** tablets is dependent on the severity of pain and the patient's previous history of analgesic requirements. One tablet to be taken every four hours or as directed by a physician. Increasing severity of pain or tolerance to morphine will require increased dosage of **Sevredol** tablets using 10 mg or 20 mg alone or in combination to achieve the desired relief.

Patients receiving **Sevredol** tablets in place of parenteral morphine should be given a sufficiently increased dosage to compensate for any reduction in analgesic effects associated with oral administration. Usually such increased requirement is of the order of 100%. In such patients, individual dose adjustments are required.

Elderly

A reduction in adult dosage may be advisable.

Paediatric population

3-5 years 5mg 4-hourly

6-12 years 5-10mg 4-hourly

Route of administration

Oral.

Treatment goals and discontinuation

Before initiating treatment with **Sevredol** tablets, 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 **Sevredol** tablets, 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

Sevredol tablets should not be used longer than necessary.

4.3 Contraindications

Morphine products are contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe chronic obstructive pulmonary disease
- Severe bronchial asthma
- Severe respiratory depression with hypoxia and/or hypercapnia
- Paralytic ileus
- Head injury
- Acute abdomen
- Delayed gastric emptying
- Known morphine sensitivity
- Acute hepatic disease
- Concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use

Not recommended during pregnancy.

Not recommended for children below 3 years of age.

4.4 Special warnings and precautions for use

Sevredol tablets should be administered with caution in patients with:

- Severely impaired respiratory function
- Respiratory depression
- Severe cor pulmonale
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Opioid Use Disorder
- Psychological dependence[addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin.
- hypotension with hypovolaemia
- hypothyroidism
- adrenocortical insufficiency
- convulsive disorders
- biliary tract disorders
- pancreatitis
- prostatic hypertrophy
- inflammatory bowel disorders
- severely impaired renal function
- severely impaired hepatic function
- severe bronchial asthma
- delirium tremens
- constipation

As with all narcotics, a reduction in dosage may be advisable in the elderly,

Sevredol tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, **Sevredol** tablets should be discontinued immediately.

Respiratory Depression

The major risk of opioid excess is respiratory depression.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent fashion. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). 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.

Morphine may lower the seizure threshold in patients with a history of epilepsy.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of **Sevredol** tablets 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 **Sevredol** tablets 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).

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.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive **Sevredol** tablets for 4 hours prior to the intervention. If further treatment with **Sevredol** tablets is indicated then the dosage should be adjusted to the new post-operative requirement. **Sevredol** tablets should be used with caution pre-operatively and within the first 24 hours post-operatively. **Sevredol** tablets should also be used with caution following abdominal surgery.

Hyperalgesia that does not respond to a further dose increase of morphine sulfate may occur, particularly in high doses. A morphine sulfate dose reduction or change in opioid may be required.

Opioid Use Disorder (abuse and dependence)

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as **Sevredol** tablets.

Repeated use of **Sevredol** tablets 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 **Sevredol** tablets 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 (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with **Sevredol** tablets 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 behaviour (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.

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

Some changes that can be seen with long-term use of opioid analgesics include an increase in serum prolactin, and decreases in plasma cortisol, oestrogen and testosterone in association with inappropriately low or normal ACTH, LH or FSH levels. Clinical symptoms include decreased libido, impotence or amenorrhea which may be manifest from these hormonal changes.

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.

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)

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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, which include, but are not limited to: other opioids, anxiolytics, sedatives and hypnotics (including benzodiazepines), antiepileptics (including gabapentinoids, e.g., pregabalin or gabapentin), general anaesthetics (including barbiturates), antipsychotics (including phenothiazines), other tranquilisers, antidepressants, muscle relaxants, antihypertensives, centrally acting anti-emetics and alcohol. 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.

Mixed agonist/antagonist opioid analgesics (e.g. buprenorphine, nalbuphine, pentazocine) should not be administered to a patient who has received a course of therapy with a pure opioid agonist analgesic.

Cimetidine inhibits the metabolism of morphine.

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis. Morphine should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

Plasma concentrations of morphine may be reduced by rifampicin (see section 4.4).

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.

Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine, and may possibly decrease plasma concentrations of morphine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Sevredol tablets are not recommended during pregnancy and labour due to the risk of neonatal respiratory depression. Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care.

Breast feeding

Administration to nursing mothers is not recommended as morphine is excreted in breast milk.

Fertility

Animal studies have shown that morphine may reduce fertility (see 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Treatment with SEVREDOL tablets may cause sedation and it is not recommended that patients drive or use machines if they experience drowsiness.

4.8 Undesirable effects

In normal doses, the commonest side effects of morphine are nausea, vomiting, constipation and drowsiness. With chronic therapy, nausea and vomiting are unusual with **Sevredol** tablets but should they occur the tablets can be readily combined with an anti-emetic if required. Constipation may be treated with appropriate laxatives.

The following frequencies are the basis for assessing undesirable effects:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

	Very Common	Common	Uncommon	Not known
Immune system disorders			Hypersensitivity	Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders		Confusion Insomnia	Agitation Euphoria Hallucinations Mood altered	Thinking disturbances Drug dependence Dysphoria
Nervous system disorders		Dizziness Headache Hyperhidrosis Involuntary muscle contractions Somnolence	Convulsions Hypertonia Paraesthesia Syncope Myoclonus	Allodynia Hyperalgesia (see section 4.4)
Eye disorders			Visual impairment	Miosis
Ear and			Vertigo	

labyrinth disorders				
Cardiac disorders			Palpitations	Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Hypertension
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema Respiratory depression Bronchospasm	Cough decreased Central sleep apnoea syndrome
Gastrointestinal disorders	Nausea Constipation	Abdominal pain Anorexia Dry mouth Vomiting	Ileus Taste perversion Dyspepsia	Pancreatitis
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis Spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders		Rash	Urticaria	Acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders			Urinary retention	Ureteric spasm
Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction
General disorders and administration site conditions		Asthenia Fatigue Malaise Pruritus	Peripheral oedema	Drug tolerance Drug withdrawal (abstinence)syndrome Drug withdrawal (abstinence)syndrome neonatal

The effects of morphine have led to its abuse and dependence may develop with regular, inappropriate use. This is not a major concern in the treatment of patients with severe pain.

Drug dependence and withdrawal (abstinence) syndrome

Repeated use of **Sevredol** tablets 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).

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. 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 section 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 HPRA Pharmacovigilance. Website: www.hpra.ie

4.9 Overdose

Signs of morphine toxicity and overdose are drowsiness, pin-point pupils, skeletal muscle flaccidity, bradycardia, hypotension respiratory depression, pneumonia aspiration, somnolence and central nervous system depression which can progress to

stupor or coma. Death may occur from respiratory failure. Circulatory failure and deepening coma may occur in more severe cases. Overdose can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdose.

Toxic leukoencephalopathy has been observed with morphine overdose.

Treatment of morphine overdose:

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdose, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established.

For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloid.

ATC code: N02A A01

Morphine acts as an agonist at opiate receptors in the CNS particularly mu and to a lesser extent kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression, and euphoria, and kappa receptors, spinal analgesia, miosis and sedation.

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis).

Morphine produces respiratory depression by direct action on brain stem respiratory centres.

Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of haemorrhagic or ischaemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation.

Cardiovascular System

Morphine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioids may affect the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal system resulting in adrenal insufficiency or hypogonadism respectively (See section 4.4).

Other Pharmacological Effects

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown.

5.2 Pharmacokinetic properties

Morphine is well absorbed from SEVREDOL tablets, however first pass metabolism does occur. Apart from the liver, metabolism also occurs in the kidney and intestinal mucosa. The major urinary metabolite is morphine-3-glucuronide but morphine-6-glucuronide is also formed. The half life for morphine in the plasma is approximately 2.5 - 3.0 hours.

5.3 Preclinical safety data

In male rats, reduced fertility and chromosomal damage in gametes have been reported. There are no further pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose (anhydrous)
Pregelatinised Maize Starch
Povidone
Magnesium stearate
Talc

Film coat

Opadry 85F240092 pink containing
Polyvinyl alcohol
Titanium dioxide E171
Macrogol 3350
Talc
Erythrosine E127
Sunset yellow E110

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVdC coated PVC blister packs and polypropylene containers with polyethylene lids containing 56 and 112 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1688/009/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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