Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sevredol 50 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg Morphine Sulfate.
Also contains 167.5 mg lactose.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pale green, film coated, biconvex, capsule-shaped tablet, marked with a scoreline with " IR" to the left and "50" 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, 20 mg or 50 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
Sevredol tablets 50 mg are not recommended in children.

Route of administration

Oral.

Discontinuation of therapy
An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore, the dose should be gradually reduced prior to discontinuation.

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)
- 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.

Opioids may 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 manner in some patients. 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.

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.

Dependence and withdrawal (abstinence) syndrome
Morphine has an abuse profile similar to other strong agonist opioids and should be used with particular caution in patients with a history of alcohol and drug abuse. Morphine may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of physical and/or psychological dependence (addiction) or tolerance to opioid analgesics, including morphine. The risk increases with the time the drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

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).

Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, sedatives and hypnotics (including benzodiazepines), antiepileptics (including gabapentinoids, e.g., pregabalin), general anaesthetics (including barbiturates),

antipsychotics (including phenothiazines), antidepressants, muscle relaxants, antihypertensives, centrally acting anti-emetics and alcohol.

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 (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 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) Sleep apnoea syndrome
Eye disorders			Visual impairment	Miosis
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations	Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Hypertension
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema Respiratory depression Bronchospasm	Cough decreased
Gastrointestinal disorders	Nausea Constipation	Abdominal pain Anorexia Dry mouth Vomiting	Ileus Taste perversion Dyspepsia	
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis
Skin and subcutaneous tissue disorders		Rash	Urticaria	
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
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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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.

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 other 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 OY-21037 green containing
Hypromellose (E464)
Titanium dioxide (E171)
Quinoline yellow (E104)
Indigo carmine (E132)
Iron oxide yellow (E172)
Macrogol 400

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

Mundipharma Pharmaceuticals Limited, United Drug House, Magna Drive, Magna Business Park, Citywest Road, Dublin 24, Ireland

8 MARKETING AUTHORISATION NUMBER

PA1688/009/003

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