PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]Sandoz Morphine SR

Morphine Sulfate Sustained Release Tablets

Tablets, 15 mg, 30 mg, 60 mg, 100 mg and 200 mg, Oral

Manufacturer's Standard

Opioid Analgesic N02AA01

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RECENT MAJOR LABEL CHANGES

7 WARNINGSAND PRECAUTIONS, General, Addiction, Abuse and Misuse	11/2022
7 WARNINGSAND PRECAUTIONS, Neurologic, Serotonin toxicity/Serotonin syndrome	02/2021
7 WARNINGSAND PRECAUTIONS, Neurologic, Opioid-induced hyperalgesia	11/2022
7 WARNINGSAND PRECAUTIONS, Respiratory, Sleep Apnea	02/2021
7 WARNINGS AND PRECAUTIONS, Respiratory, Acute Chest Syndrome (ACS) in Patients with Sickle Cell Disease	11/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Morphine SR (morphine sulfate sustained release tablets) is indicated for:

- the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:
  - that is opioid-responsive, and
  - for which alternative treatment options are inadequate

Sandoz Morphine SR is not indicated as an as-needed (prn) analgesic.

1.1 Pediatrics

Pediatrics (<18 years of age):
Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Sandoz Morphine SR in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use. Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history (see 10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years of age):
Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see 10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics).

2 CONTRAINDICATIONS

Sandoz Morphine SR is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).

- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).

- Patients with mild, intermittent or short duration pain that can be managed with other pain medications.

- The management of acute pain, including use in outpatient or day surgeries.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, with hypoxia and/or hypercapnia, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, brain tumor and/or head injury.
- Patients with cardiac arrhythmias.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7.1.1 Pregnant Women, and 7.1.2 Breast-feeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Limitations of Use

  Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with sustained release opioid formulations, Sandoz Morphine SR (morphine sulfate sustained release tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see 4.1 Dosing Considerations).

- Addiction, Abuse, and Misuse

  Sandoz Morphine SR pose risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Sandoz Morphine SR, and all patients should be monitored regularly for the development of these behaviours or conditions (see 7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse). Sandoz Morphine SR should be stored securely to avoid theft or misuse.

- Life-threatening Respiratory Depression: OVERDOSE

  Serious, life-threatening, or fatal respiratory depression may occur with use of Sandoz Morphine SR. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Sandoz Morphine SR or following a dose increase (see 7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression).

Sandoz Morphine SR 15 mg, 30 mg, 60 mg and 100 mg tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Sandoz Morphine SR can lead to rapid release and absorption of a potentially fatal dose of morphine . Further, instruct patients of the hazards related to taking opioids including fatal overdose. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.

- Accidental Exposure

  Accidental ingestion of even one dose of Sandoz Morphine SR, especially by children, can result in a fatal overdose of morphine (see 11 STORAGE, STABILITY AND DISPOSAL, for instructions on proper disposal).

- Neonatal Opioid Withdrawal Syndrome

  Prolonged maternal use of Sandoz Morphine SR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome (NOWS)).

- Interaction with Alcohol

  The co-ingestion of alcohol with Sandoz Morphine SR should be avoided as it may result in dangerous additive effects, causing serious injury or death (see 7 WARNINGS AND PRECAUTIONS, General and 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

- Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

  Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 7 WARNINGS AND PRECAUTIONS, Neurologic and 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

  - Reserve concomitant prescribing of Sandoz Morphine SR and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
  - Limit dosages and durations to the minimum required.
  - Follow patients for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 90 mg daily of Sandoz Morphine SR not be exceeded. Each patient should be assessed for their risk prior to prescribing Sandoz Morphine SR, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of Sandoz Morphine SR (see 4.2 Recommended Dose and Dosage Adjustment).**

- **Sandoz Morphine SR should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.**

- **Sandoz Morphine SR 15, 30, 60 and 100 mg tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving Sandoz Morphine SR can lead to the rapid release and absorption of a potentially fatal dose of morphine. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact (see 7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse).**

- Administration and dosing of morphine should be individualized bearing in mind the properties of the drug. In addition, the nature and severity of the pain or pains experienced, and the total condition of the patient must be taken into account. Of special importance is other medication given previously or concurrently.

- As with other opioid analgesics, use of morphine for the management of persistent pain should be preceded by a thorough assessment of the patient and diagnosis of the specific pain or pains and their causes. Use of opioids for the relief of chronic pain, including cancer pain, all important as it may be, should be only one part of a comprehensive approach to pain control including other treatment modalities or drug therapy, non-drug measures and psychosocial support.

- Sandoz Morphine SR should be used with caution within 24 hours pre-operatively and within the first 24 hours post-operatively (see 7 WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

- Sandoz Morphine SR tablets are not indicated for rectal administration.

4.2 Recommended Dose and Dosage Adjustment

- Pediatrics (< 18 years of age)

  Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history.

  An appropriate initial dose for children inadequately controlled on non-opioids or weak opioids is 0.5-1 mg/kg Sandoz Morphine SR orally every 12 hours.

- Adults (≥ 18 years of age)

  Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, and medical and analgesic history.

  The most frequent initial dose is 30 mg orally every 12 hours.

- Patients over the Age of 50

  Patients over 50 years of age tend to require much lower doses of morphine than in younger adults.

- Geriatrics (> 65 years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and slowly titrated, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy.

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration (see 7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics)

- Patients Not Receiving Opioids at the Time of Initiation of Sandoz Morphine SR Treatment

  The usual initial adult dose of Sandoz Morphine SR for patients who have not previously received opioid analgesics is 30 mg orally, every 12 hours.

- Patients Currently Receiving Opioids

  Patients currently receiving other oral morphine formulations may be transferred to Sandoz Morphine SR at the same total daily morphine dosage, equally divided into two 12 hourly Sandoz Morphine SR doses.

  For patients who are receiving an alternate opioid, the "oral morphine sulfate equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, Table 1 (below) can be used to calculate the approximate daily oral morphine sulfate dosage that should provide equivalent analgesia. This total daily oral morphine dosage should then be equally divided into two 12 hourly Sandoz Morphine SR doses. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

- Patients with Hepatic Impairment

  Dosage reduction is recommended in severe hepatic impairment due to the risk of toxicity (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

- Patients with Renal Impairment

  Dosage reduction is recommended in severe renal impairment due to the risk of toxicity (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

- Opioid Rotation

  Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, **consider reducing the calculated dose by 25-50%** to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1 - Opioid Conversion Table[a]

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	Daily 90 mg MED[b]
Morphine	1	1	90 mg
Codeine	0.15	6.67	600 mg
Hydromorphone	5	0.2	18 mg

Oxycodone	1.5	0.667	60 mg
Tapentadol	0.3-0.4	2.5-3.33	300 mg
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

a. Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017
b. MED: Morphine Equivalent Dose

- Debilitated Patients

  In debilitated patients and those with impaired respiratory function or significantly decreased hepatic and/or renal function, morphine should be administered with caution and at a reduced dosage (see 7.1 Special Populations and 10.3 Pharmacokinetics, Special Populations and Conditions).

- Use with Non-Opioid Medications

  If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Sandoz Morphine SR can be safely used concomitantly with usual doses of other non-opioid analgesics.

- Dose Titration

  Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at regular administration of the lowest dose of sustained release morphine (Sandoz Morphine SR) which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

  Dose adjustments should be based on the patient's clinical response. Higher doses, at certain times, may be justified in some patients to cover periods of physical activity.

  Because of the sustained release properties of Sandoz Morphine SR, dosage adjustments should generally be separated by 48 hours. If dose increments turn out to be required, they should be proportionately greater at the lower dose level (in terms of percentage of previous dose), than when adjusting a higher dose. The usual recommended dose (q12h) increments for Sandoz Morphine SR tablets are 15, 30, 45, 60, 90, 120, 150, 180 and 200 mg. Above the 200 mg/dose (400 mg/day) increments should be by 30-60 mg/dose.

  Sandoz Morphine SR is designed to allow 12 hourly dosing. If pain repeatedly occurs at the end of a dose interval, it is generally an indication for a dosage increase, rather than more frequent administration of sustained release morphine (Sandoz Morphine SR). However, where judged necessary for optimization of drug effects, Sandoz Morphine SR tablets may be administered q8h. More frequent (than q8h) administration is not recommended.

- Adjustment or Reduction of Dosage

  Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Sandoz Morphine SR. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose,

sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or improved mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Tapering should be individualized and carried out under medical supervision.

Patients should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, post-herpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

- Management of Patients Requiring Rescue Medication

  Some patients taking Sandoz Morphine SR according to a fixed time schedule may require immediate-release analgesics as "rescue" medication for pain. Selection of rescue medication should be based on individual patient conditions. Sandoz Morphine SR is a sustained release formulation and therefore is not intended for use as rescue medication.

4.3 Administration

Sandoz Morphine SR sustained release tablets may be taken with or without food, with a glass of water.

4.4 Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

5 OVERDOSAGE

- Symptoms

Serious overdosage with morphine may be characterized by respiratory depression (respiratory rate and / or tidal volume; Cheyne-Stokes respiration; cyanosis), dizziness, confusion, extreme somnolence progressing to stupor or coma, pneumonia aspiration, miosis, rhabdomyolysis progressing to renal failure, hypotonia, cold and clammy skin, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy and sometimes bradycardia and hypotension. Pinpoint pupils are a sign of narcotic overdose, but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen

with hypoxia in the setting of morphine overdose. Severe overdosage may result in apnea, circulatory collapse, cardiac arrest and death.

- Treatment

Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous adult dose of naloxone is 0.4 mg or higher. Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine, particularly sustained release formulations, may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonist should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated. In an individual physically dependent on opioids, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care by using dosage titration, commencing with 10 % to 20 % of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug, particularly when a sustained release oral formulation has been taken.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Sustained Release Tablets / 15, 30, 60, 100 and 200 mg	15 mg: FD&C blue #1 brilliant blue FCF aluminum lake, FD&C yellow #5 tartrazine aluminum lake, hypromellose, lactose anhydrous, magnesium stearate, polyethylene glycol, polyvinyl alcohol, stearic acid, talc and titanium dioxide. 30 mg: D&C red #7 lithol rubin B calcium, lake, FD&C blue #1 brilliant blue FCF Aluminum lake, hypromellose, lactose anhydrous, magnesium stearate, polyethylene glycol, polyvinyl alcohol, stearic acid, talc and titanium dioxide. 60 mg: FD&C yellow #6 sunset yellow FCF aluminum lake, hypromellose, lactose anhydrous, magnesium stearate, polyethylene glycol, polyvinyl alcohol, stearic acid, talc and titanium dioxide. 100 mg: FD&C Blue #2/ Indigo Carmine AL 3%-5%, ferrosoferric oxide/black iron oxide, hypromellose, iron oxide yellow, lactose anhydrous, magnesium stearate, polyethylene glycol, polyvinyl alcohol, stearic acid, talc and titanium dioxide. 200 mg: Erythrosine Aluminum Lake, FD&C Blue #2/ Indigo Carmine Aluminum Lake, FD&C Yellow #6/ Sunset Yellow FCF Aluminum Lake, hypromellose, lactose anhydrous, magnesium stearate, polyethylene glycol, polyvinyl alcohol, stearic acid, talc and titanium dioxide.

- Dosage Forms

  Sandoz Morphine SR 15 mg are green, oval, bi-convex, film-coated tablets imprinted with 15 on one side and rph on the other side.

  Sandoz Morphine SR 30 mg are purple, oval, biconvex, film-coated tablets imprinted with 30 on one side and rph on the other side.

Sandoz Morphine SR 60 mg are oval, orange, biconvex, film-coated tablets and imprinted with 60 on one side and rph on the other side.

Sandoz Morphine SR tablets are 100 mg, gray, round, biconvex film-coated tablets, imprinted with 100 on one side and plain on the other side.

Sandoz Morphine SR (morphine sustained release) tablets 200 mg are, red, oval, biconvex film-coated tablets, imprinted with 200 on one side and with a bisect on the other side. The 200 mg tablet may be broken in half.

- Packaging

  Sandoz Morphine SR 15, 30, 60 mg tablets are supplied in bottles of 100 tablets.

  Sandoz Morphine SR 100 and 200 mg tablets are supplied in bottles of 50 tablets

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

Patients should be instructed not to give Sandoz Morphine SR to anyone other than for whom it was prescribed, as such, inappropriate use may have severe medical consequences, including death. Sandoz Morphine SR should be stored securely to avoid theft or misuse.

Sandoz Morphine SR 15, 30, 60 and 100 mg tablets must be swallowed whole, and must not be cut, chewed, dissolved or crushed. Taking cut, broken, chewed, dissolved or crushed tablets could lead to the rapid release and absorption of a potentially fatal dose of morphine. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.

Sandoz Morphine SR 100 mg and 200 mg tablets are for use in opioid tolerant patients only (see also 4 DOSAGE AND ADMINISTRATION). These tablet strengths may cause fatal respiratory depression if administered to patients not previously exposed to daily morphine equivalent dosages of 200 mg or more. Care should be taken in the prescribing of these tablet strengths.

Patients should be cautioned not to consume alcohol while taking Sandoz Morphine SR as it may increase the chance of experiencing dangerous side effects.

Hyperalgesia that will 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.

- Addiction, Abuse and Misuse

  Like all opioids, Sandoz Morphine SR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Sandoz Morphine SR should be prescribed and handled with caution. Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Sandoz Morphine SR, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Sandoz Morphine SR is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury, which may also be fatal.

- Patient Counselling Information

A patient information sheet should be provided to patients when Sandoz Morphine SR is dispensed to them. Patients receiving Sandoz Morphine SR should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.
2. Patients should be advised that Sandoz Morphine SR contains morphine, an opioid pain medicine.
3. Patients should be advised that Sandoz Morphine SR should only be taken as directed. The dose of Sandoz Morphine SR should not be adjusted without consulting with a physician. Sandoz Morphine SR must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal morphine overdose. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.
4. Patients should be advised to report episodes of pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
5. Patients should not combine Sandoz Morphine SR with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur resulting in serious injury or death.
6. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with Sandoz Morphine SR.
7. Patients should be advised that if they have been receiving treatment with Sandoz Morphine SR and cessation of therapy is indicated, it may be appropriate to taper the Sandoz Morphine SR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
8. Patients should be informed that Sandoz Morphine SR could cause seizures if they are at risk for seizure or have epilepsy. Patients should be advised not to take Sandoz Morphine SR if they have seizure disorders. Patients should be advised to stop taking Sandoz Morphine SR if they have a seizure while taking Sandoz Morphine SR and seek medical help immediately.
9. Patients should be advised of the most common adverse reactions that may occur while taking morphine sulfate sustained release tablets: constipation, dizziness, hyperhidrosis, nausea, sedation and vomiting. If symptoms worsen, seek immediate medical attention.
10. Patients should be advised that Sandoz Morphine SR may cause drowsiness, dizziness, or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).

Patients started on Sandoz Morphine SR or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of Sandoz Morphine SR.

11. Patients should be advised that Sandoz Morphine SR is a potential drug of abuse. They should protect it from theft or misuse.
12. Patients should be advised that Sandoz Morphine SR should never be given to anyone other than the individual for whom it was prescribed.
13. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with Sandoz Morphine SR. Women who are breast-feeding or pregnant should not use Sandoz Morphine SR.

Cardiovascular

- Hypotension

  Morphine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anaesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Sandoz Morphine SR.

  The use of Sandoz Morphine SR in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Sandoz Morphine SR and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, goosef lesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see 8 ADVERSE REACTIONS, 4.2 Recommended Dosage and Dosage Adjustment).

Physical dependence with or without psychological dependence tends to occur with chronic administration. An abstinence syndrome may be precipitated when opioid administration is discontinued or opioid antagonists administered. With appropriate medical use of opioids and gradual withdrawal from the drug, these symptoms are usually mild.

- Use in Drug and Alcohol Addiction

  Sandoz Morphine SR is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Sandoz Morphine SR; extreme caution and awareness is warranted to mitigate the risk.

- In Vitro Dissolution Studies of Interaction with Alcohol

  Increasing concentrations of alcohol in the dissolution medium resulted in a decrease in the rate of release of morphine from Sandoz Morphine SR tablets. The clinical significance of these findings is unknown.

Driving and Operating Machinery

Sandoz Morphine SR may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol

Endocrine and Metabolism

- Adrenal Insufficiency

  Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal

Morphine and other morphine-like opioids have been shown to decrease bowel motility. Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions and is also contraindicated in patients with paralytic ileus, appendicitis and pancreatitis. Morphine may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease for worsening symptoms (see 2 CONTRAINDICATIONS and 8.1 Adverse Reaction Overview, Nausea and Vomiting, and 8.1 Adverse Reaction Overview, Constipation).

Neurologic

- Interactions with CNS Depressants (including benzodiazepines and alcohol)

Morphine should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation or coma may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. Sandoz Morphine SR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Sandoz Morphine SR is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see 9.5 Drug-Food Interactions).

Sandoz Morphine SR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 CONTRAINDICATIONS and 8.1 Adverse Reaction Overview, Sedation, and 9.2 Drug Interactions Overview, Interactions with Central Nervous Systems (CNS) Depressants (including benzodiazepines and alcohol)).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

- Use in Patients with Convulsive or Seizure Disorders

  The morphine sulfate in Sandoz Morphine SR may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Therefore, Sandoz Morphine SR should not be used in these patients (see 2 CONTRAINDICATIONS).

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

- Serotonin Toxicity / Serotonin Syndrome

Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with morphine, including Sandoz Morphine SR, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions, Serotonergic Agents).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with Sandoz Morphine SR and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions, Serotonergic Agents). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

- Head Injury

  The respiratory depressant effects of morphine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Opioid analgesics, including morphine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine should not be used (see 2 CONTRAINDICATIONS).

- Opioid-induced hyperalgesia

  Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra- operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful) stimuli (allodynia) in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

Peri-Operative Considerations

Sandoz Morphine SR is not recommended for preoperative use or postoperatively within the first 24 hours.

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Sandoz Morphine SR for at least 24 hours before the operation and Sandoz Morphine SR should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate.

Thereafter, if Sandoz Morphine SR is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for

pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Morphine (and other morphine-like opioids) has been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Reproductive Health: Female and Male Potential

- **Fertility**

  Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see 8.5 Post-Market Adverse Reactions).

- **Teratogenic Risk**

  - Neonatal Opioid Withdrawal Syndrome (NOWS)

    Prolonged maternal use of opioid during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

    Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

    Use of Sandoz Morphine SR is contraindicated in pregnant women (see 2 CONTRAINDICATIONS).

Respiratory

- Respiratory Depression

  Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

  While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Sandoz Morphine SR, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Sandoz Morphine SR and following dose increases. Morphine should be used with extreme caution in patients with substantially decreased respiratory

reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see 2 CONTRAINDICATIONS).

To reduce the risk of respiratory depression, proper dosing and titration of Sandoz Morphine SR are essential. Overestimating the Sandoz Morphine SR dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see 7.1 Special Populations, Special Risk Groups, and 4.2 Recommended Dose and Dosage Adjustment).

Sandoz Morphine SR 100 mg and 200 mg tablets are for use in opioid tolerant patients only (see 4 DOSAGE AND ADMINISTRATION). These tablet strengths may cause fatal respiratory depression if administered to patients not previously exposed to daily morphine equivalent dosages of 200 mg or more. Care should be taken in the prescribing of these tablet strengths.

- Use in Patients with Chronic Pulmonary Disease

  Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Sandoz Morphine SR, as in these patients, even usual therapeutic doses of Sandoz Morphine SR may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Sandoz Morphine SR is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see 2 CONTRAINDICATIONS).

- Sleep Apnea

  Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, and 4.2 Recommended Dose and Dosage Adjustment).

- 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.

7.1 Special Populations

- Special Risk Groups

  Sandoz Morphine SR should be administered with caution to patients with a history of alcohol, seizures, and drug abuse and in a reduced dosage to elderly or debilitated patients, patients with reduced hepatic function or severe renal dysfunction, and to patients with adrenocortical insufficiency (e.g., Addison's disease), biliary tract disorders, hypotension with hypovolaemia, hypothyroidism, prostatic hypertrophy or urethral stricture.

The administration of opioid analgesics, including morphine, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Opioid analgesics including morphine should also be used with caution in patients about to undergo surgery of the biliary tract, since it may cause spasm of the sphincter of Oddi.

7.1.1 Pregnant Women

Animal studies with morphine and other opioids have indicated the possibility of teratogenic effects. In humans, it is not known whether morphine can cause fetal harm when administered during pregnancy or can affect reproductive capacity. Since morphine crosses the placental barrier, Sandoz Morphine SR is contraindicated in patients who are pregnant (see 2 CONTRAINDICATIONS).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome (NOWS), and 8.5 Post-Market Adverse Reactions).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complications such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

7.1.2 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, Sandoz Morphine SR is contraindicated in nursing women during labour and delivery. Life-threatening respiratory depression may occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Sandoz Morphine SR is used in this population.

7.1.3 Pediatrics

- Pediatrics (< 18 years of age)

  Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history.

  An appropriate initial dose for children inadequately controlled on non-opioids or weak opioids is 0.5 - 1 mg/kg Sandoz Morphine SR orally every 12 hours.

7.1.4 Geriatrics

- Geriatrics (> 65 years of age)

  In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrated slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 4.2 Recommended Dose and Dosage Adjustment, and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

Patients over 50 years of age tend to require much lower doses of morphine than in the younger age group.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects of Sandoz Morphine SR are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and, to a lesser degree, circulatory depression respiratory arrest, shock and cardiac arrest.

The most frequently observed side effects of morphine sulfate sustained release tablets are constipation, dizziness, hyperhidrosis, nausea, sedation and vomiting.

- Sedation

Some degree of sedation is experienced by most patients upon initiation of therapy. This may be at least partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusion. If excessive sedation persists, the reason for it must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated in an older patient, or the patient is actually more severely ill than realized. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

- Nausea and Vomiting

Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

- Constipation

Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management

at the start of prolonged opioid therapy. Stool softeners, stimulant laxatives and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following adverse effects occur with morphine sulfate sustained release tablets and opioid analgesics. The reactions are categorized by body system and frequency according to the following definitions: Very common (≥ 1/10); (Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

- General Disorders and Administration Site Conditions:
  - Common: asthenia, fatigue, malaise, pruritus, weakness, sedation
  - Uncommon: peripheral edema
  - Not known: drug tolerance, drug withdrawal syndrome, drug withdrawal syndrome neonatal

- Cardiac Disorders:
  - Uncommon: palpitations
  - Rare: faintness
  - Unknown: supraventricular tachycardia, bradycardia

- Ear and Labyrinth Disorders:
  - Uncommon: vertigo

- Endocrine Disorders: A syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary).

- Eye Disorders:
  - Uncommon: visual disturbance
  - Not known: miosis

- Gastrointestinal Disorders:
  - Very common: constipation, nausea
  - Common: abdominal pain, anorexia, dry mouth, vomiting
  - Uncommon: dyspepsia, ileus, taste perversion

- Hepato-biliary Disorders:
  - Uncommon: increased hepatic enzyme
  - Not known: biliary pain, exacerbation of pancreatitis

- Immune System Disorders:
  - Uncommon: hypersensitivity

- Not known: anaphylactic reaction, anaphylactoid reaction

- Nervous System Disorders:
  - Common: dizziness, headache, involuntary muscle contractions, somnolence
  - Uncommon: convulsions, hypertonia, paraesthesia, syncope, myoclonus
  - Not known: allodynia, hyperalgesia, obstructive sleep apnea syndrome

- Psychiatric Disorders:
  - Common: confusion, insomnia
  - Uncommon: agitation, euphoria, hallucinations, mood altered
  - Not known: drug dependence, dysphoria, thinking disturbances

- Renal and Urinary Disorders:
  - Uncommon: urinary retention
  - Unknown: ureteric spasm

- Respiratory, Thoracic and Mediastinal Disorders:
  - Uncommon: bronchospasm, pulmonary edema, respiratory depression
  - Not known: cough decreased

- Reproductive System and Breast Disorders:
  - Not known: amenorrhoea, decreased libido, erectile dysfunction

- Skin and Subcutaneous Tissue Disorders:
  - Common: hyperhidrosis, rash
  - Uncommon: urticaria

- Vascular Disorders:
  - Uncommon: facial flushing, hypotension
  - Unknown: hypertension

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of morphine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Adrenal insufficiency

  Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

- Androgen deficiency

  Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

- Serotonin syndrome

  Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

There have also been post-marketing reports of Neonatal Opioid Withdrawal Syndrome (NOWS) in patients treated with hydromorphone (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk, Neonatal Opioid Withdrawal Syndrome (NOWS)).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Risks from concomitant use of opioids and benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see 7 WARNINGS AND PRECAUTIONS)
  - Reserve concomitant prescribing of Sandoz Morphine SR and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate
  - Consider dose reduction of CNS depressants in situations of concomitant prescribing
  - Follow patients for signs and symptoms of respiratory depression and sedation
- MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. Sandoz Morphine SR is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days.

9.2 Drug Interactions Overview

- Interactions with CNS Depressants (including benzodiazepines and alcohol)

  Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics gabapentin, pregabalin, baclofen, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Monitor patients closely for signs of respiratory depression and sedation (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol) and 7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery). Sandoz Morphine SR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

9.3 Drug-Behavioural Interactions

The concomitant use of alcohol should be avoided (see 7 WARNINGS AND PRECAUTIONS, General).

9.4 Drug-Drug Interactions

Generally, the effects of morphine may be antagonized by acidifying agents and potentiated by alkalizing agents. The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol.

- Warfarin and Other Coumarin Anticoagulants

  Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

- Administration with Mixed Activity Agonist/Antagonist Opioids

  Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as morphine. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of morphine and/or may precipitate withdrawal symptoms in these patients.

- MAO Inhibitors

  Monoamine oxidase inhibitors (MAO) intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. Sandoz Morphine SR is contraindicated in patients receiving MAO inhibitors or who have taken them within the previous 14 days (see 2 CONTRAINDICATIONS).

- Serotonergic Agents

  Coadministration of morphine sulfate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

9.5 Drug-Food Interactions

Food has no significant effect on the extent of absorption of morphine from Sandoz Morphine SR.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Morphine is an opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, morphine produces a variety of effects including analgesia, constipation from decreased gastrointestinal motility, suppression of the cough reflex, respiratory depression from reduced responsiveness of the respiratory center to CO_2, nausea and vomiting via stimulation of the CTZ, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

10.2 Pharmacodynamics

Morphine is readily absorbed from the gastrointestinal tract, nasal mucosa, lung, and after subcutaneous or intramuscular injection. Due to first-pass metabolism the effect of an oral dose is less than that of the same dose given parenterally. The parenteral to oral morphine potency ratio has been reported to range from 1:6 to 1:2. In general, the greatest difference between parenteral and oral potency is seen in acute studies. With chronic dosing, oral morphine is about 1/3 as potent as when given by injection.

Absorption of the sustained-release tablets is equivalent to that of immediate-release tablet or liquid formulations and is not significantly affected by administration with food. At steady-state, the sustained-release tablets produce peak morphine levels approximately 4 to 5 hours post-dose and therapeutic levels persist for a 12 hour period.

In a steady-state crossover study utilizing morphine sulfate sustained release tablets every 12 hours versus morphine sulfate solution every 4 hours in cancer patients, there was no significant difference between formulations in respect to the extent of absorption of morphine. The mean maximum concentration following morphine sulfate sustained release tablets was approximately 15% higher than with morphine oral solution and was achieved at a mean of 3.4 hours post-dose compared with 1.2 hours for the solution. There was a linear relationship between mean plasma morphine concentration and dose over the range of 60-600 mg/day.

Morphine is an opioid agonist. Adequate doses will relieve even the most severe pain. Clinically however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, nausea and vomiting, which can result from high doses.

- 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.

- Central Nervous System

  In man, the principal pharmacological actions of morphine are in the CNS; analgesia, drowsiness, mood changes, mental clouding, respiratory depression, nausea or emesis and miosis.

  Morphine produces respiratory depression by direct action on brain stem respiratory centres. It 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 hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

- Endocrine System

  Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

- 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. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

- Hepatobiliary System

  Opioids may induce biliary spasm.

- Immune System

  In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

- Concentration – Efficacy Relationships

  Morphine induced analgesia is a result of increases in both the pain threshold and pain tolerance. Morphine alters the affective response to pain in that patients remain aware of its existence but are less distressed. Morphine relieves most types of pain but is more effective against dull constant pains than sharp intermittent ones.

- Concentration – Adverse Reaction Relationship

  There is a significant relationship between increasing morphine plasma concentrations and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related side effects.

  The dose of Sandoz Morphine SR must be individualized (see 4 DOSAGE AND ADMINISTRATION) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

10.3 Pharmacokinetics

With repeated regular dosing, oral morphine is about 1/3 as potent as when given by intramuscular injection. The relationship between mean plasma concentration and dose has been shown to be linear over a dosage range of 60 - 600 mg/day in the case of the morphine sulfate sustained release tablets.

Absorption:

Morphine is readily absorbed when given orally, rectally or by subcutaneous or intramuscular injection. Due to "first-pass" metabolism in the liver, the effect of an oral dose is less than after parenteral administration.

When administered every 12 hours, the sustained-release tablets provide equivalent analgesia to morphine oral solution given 4 hourly. In most cases, administration on a twelve hourly schedule produces equivalent pain control to eight hourly administration.

Distribution:

Following absorption, approximately 30% to 35% of morphine is reversibly bound to plasma proteins. Free morphine readily leaves the circulation and is concentrated in the liver, kidney, lung, spleen and, to a lesser extent, skeletal muscle. In adults, only small quantities of morphine pass the blood brain barrier. Morphine also crosses the placental membranes and has been found in breast milk (see 7.1.1 Pregnant Women, and 7.1.2 Breast-feeding).

Metabolism:

Conjugated morphine excreted in the bile may be hydrolyzed and reabsorbed from the large bowel. Conjugation with glucuronic acid is the major metabolic pathway for morphine.

The major metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Minor metabolites include normorphine, morphine-3-6 diglucuronide and morphine-3-ethereal sulfate.

The mean elimination half-life of morphine is 2 to 3 hours with great inter-patient variability.

Elimination:

The major route of elimination is via the kidney. Morphine is primarily excreted in the urine as morphine-3-glucuronide. About 7% to 10% of a dose of morphine is excreted in the feces via the bile.

Special Populations and Conditions

- Pediatrics (< 18 years of age)

  Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history.

- Geriatrics (> 65 years of age)

Dose selection for an elderly patient should be cautious, usually starting at one half the recommended adult dose, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 7.1.4 Geriatrics).

- Hepatic Insufficiency

  The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. M3G and M6G to morphine plasma AUC ratios also decreased in these patients, indicating a decrease in metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment).

- Renal Insufficiency

  The pharmacokinetics of morphine are altered in patients with renal failure. The AUC is increased and clearance is decreased. Metabolites, M3G and M6G, accumulate several-fold in patients with renal failure compared to healthy subjects. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Renal Impairment).

11 STORAGE, STABILITY AND DISPOSAL

- Storage

  Store between 15-30°C. Protect from light. Protect from moisture.

- Disposal

  Sandoz Morphine SR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Sandoz Morphine SR should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. Sandoz Morphine SR should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

12 SPECIAL HANDLING INSTRUCTIONS

Sandoz Morphine SR should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. Sandoz Morphine SR should not be used in front of children, since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

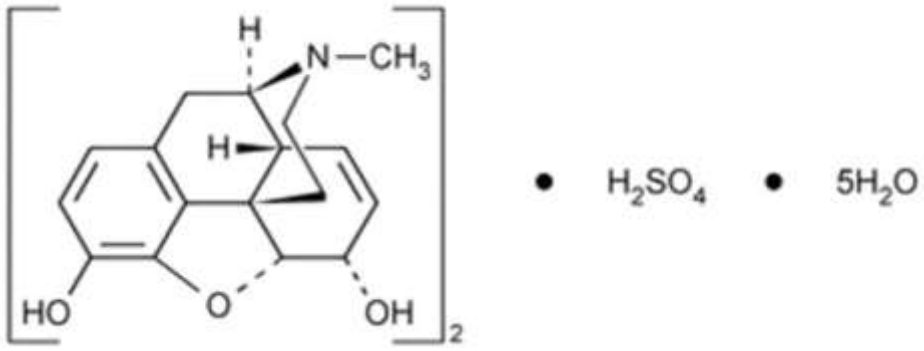
Proper Name: Morphine Sulfate

Chemical Name: 7,8,-didehydro-4,5 α-epoxy-17-methyl-morphinan-3, 6α-diol sulfate (2:1) (salt) pentahydrate

Molecular Formula and molecular mass: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$

758.8 g/mol (pentahydrate)
668.8 g/mol (anhydrous)

Structural Formula:



Physicochemical Properties: Morphine is a phenanthrene alkaloid obtained from opium.

Product Characteristics

- Physical Description:

  Morphine sulfate is a white, odourless crystalline powder or needle-like crystals.

- Solubility:

  Soluble 1:21 in water and 1:1000 in ethanol. It is practically insoluble in ether or chloroform.

- Melting Point:

  Approximately 250° C (decomposes when anhydrous)

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

14.3 Comparative Bioavailability Studies

Randomized, two-way crossover, single-dose bioavailability studies were conducted in fasting and fed, healthy adult male subjects. The bioavailability of Morphine SR sustained-release tablets, 15, 30 and 60 mg, relative to MS Contin® sustained-release tablets, 15, 30 and 60 mg was determined following single 2 x 15 mg, 1 x 30 mg and 1 x 60 mg doses. In addition, comparative bioavailability studies in healthy adult male subjects under steady-state conditions were conducted on each morphine sulfate strength. The average values of the pharmacokinetic parameters as well as ratio of means (with 90% confidence intervals) are listed in the following tables:

Table 1:

Summary Table of the Comparative Bioavailability Study of Morphine SR vs MS Contin®, Morphine Sulfate 15 mg tablets conducted under single-dose fasting conditions in 20 healthy adult male volunteers From measured data

Geometric Mean Arithmetic Mean (CV %)

Parameter	Test[1] Morphine SR	Reference[2] MS Contin®	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng.h/mL)	67.59 69.45 (24.4)	66.50 68.06 (22.5)	102	(97-106)
AUC_I (ng.h/mL)	79.99 82.66 (26.1)	78.52 80.36 (22.1)	102	(97-107)
AUC_{0-12}	52.39 53.76 (24.7)	51.93 53.40 (25.3)	101	(95-107)
C_{MAX} (ng/mL)	9.19 9.75 (45.0)	10.40 10.88 (32.7)	88	(80-98)
T_{MAX}[3] (h)	2.23 (47.5)	2.14 (45.6)	---	---
$T_{½}$[3] (h)	9.37 (24.3)	9.75 (28.9)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and T1/2 parameters are expressed as the arithmetic means (CV%) only.

Table 2:

Summary Table of the Comparative Bioavailability Study
of Morphine SR vs MS Contin®, Morphine Sulfate 15 mg tablets conducted under single-
dose fed conditions in 19 healthy adult male volunteers
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	**Test**[1] Morphine SR	**Reference**[2] MS Contin®	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (ng.h/mL)	81.24 82.83 (21.2)	79.23 81.10 (23.5)	103	(99-106)
AUC_I (ng.h/mL)	96.57 98.68 (22.3)	97.05 100.07 (27.1)	100	(95-105)
AUC_{0-12}	64.36 65.79 (22.0)	63.34 64.43 (20.7)	102	(97-107)
C_{MAX} (ng/mL)	12.93 13.49 (28.4)	12.24 12.54 (25.1)	106	(91-123)
T_{MAX}[3] (h)	2.68 (39.4)	2.47 (43.9)	---	---
$T_{½}$[3] (h)	10.45 (26.8)	11.87 (36.7)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and T1/2 parameters are expressed as the arithmetic means (CV%) only.

Table 3:

Summary Table of the Comparative Bioavailability Study
of Morphine SR vs MS Contin®, Morphine Sulfate 15 mg tablets conducted under steady-state conditions in 18 healthy adult male volunteers
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	**Test**[1] Morphine SR	**Reference**[2] MS Contin®	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_{λ} (ng.h/mL)	53.00 54.08 (23.49)	54.11 55.29 (27.19)	97.9	(93.3-102.8)
C_{MAX} (ng/mL)	7.54 7.80 (27.39)	8.41 8.66 (29.53)	89.7	(80.7-99.7)
C_{MIN} (ng/mL)	1.94 1.98 (24.93)	1.89 1.97 (33.05)	102.4	(92.9-112.9)
T_{MAX}[3] (h)	2.50 (54.38)	2.50 (36.38)	---	---
Fluctuation[3] (%)	128.39 (20.24)	146.43 (20.29)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and Fluctuation parameters are expressed as the arithmetic means (CV%) only.

Table 4:

Summary Table of the Comparative Bioavailability Study
of Morphine SR vs MS Contin®, Morphine Sulfate 30 mg tablets conducted under single-
dose fasting conditions in 18 healthy adult male volunteers
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	**Test**[1] Morphine SR	**Reference**[2] MS Contin®	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (ng.h/mL)	72.50 74.37 (22.8)	72.92 74.74 (22.4)	100	(96-104)
AUC_I (ng.h/mL)	88.05 90.24 (22.0)	86.73 88.75 (22.1)	102	(97-109)
AUC_{0-12}	54.31 55.90 (24.5)	57.27 59.18 (25.3)	95	(90-100)
C_{MAX} (ng/mL)	9.49 9.83 (29.1)	10.71 11.00 (24.0)	89	(83-95)
T_{MAX}[3] (h)	2.16 (35.6)	2.21 (50.6)	---	---
$T_{½}$[3] (h)	10.18 (26.5)	9.71 (48.3)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and T1/2 parameters are expressed as the arithmetic means (CV%) only.

Table 5:

Summary Table of the Comparative Bioavailability Study of Morphine SR vs MS Contin®, Morphine Sulfate 30 mg tablets conducted under fed conditions in 20 healthy adult male volunteers From measured data

Geometric Mean Arithmetic Mean (CV %)

Parameter	Test[1] Morphine SR	Reference[2] MS Contin®	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng.h/mL)	80.44 83.37 (28.2)	81.58 83.91 (24.1)	99	(93-105)
AUC_I (ng.h/mL)	92.13 95.05 (26.0)	96.27 98.89 (23.7)	96	(90-102)
AUC_{0-12}	63.37 66.00 (30.7)	63.89 65.80 (24.5)	99	(93-106)
C_{MAX} (ng/mL)	11.85 13.80 (72.3)	11.87 12.54 (35.6)	100	(84-119)
T_{MAX}[3] (h)	2.97 (35.0)	3.10 (45.2)	---	---
$T_{½}$[3] (h)	8.27 (24.8)	9.72 (22.9)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and T1/2 parameters are expressed as the arithmetic means (CV%) only.

Table 6:

Summary Table of the Comparative Bioavailability Study
of Morphine SR vs MS Contin®, Morphine Sulfate 30 mg tablets conducted under steady-state conditions in 15 healthy adult male volunteers
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	**Test**[1] Morphine SR	**Reference**[2] MS Contin®	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_{λ} (ng.h/mL)	114.94 116.90 (19.83)	114.29 117.50 (23.06)	100.6	(94.4-107.2)
C_{MAX} (ng/mL)	15.90 16.42 (27.24)	17.24 17.81 (26.71)	92.2	(85.8-99.1)
C_{MIN} (ng/mL)	4.41 4.45 (16.42)	4.01 4.19 (29.34)	110.1	(96.4-125.6)
T_{MAX}[3] (h)	3.00 (38.94)	3.00 (50.57)	---	---
Fluctuation[3] (%)	122.14 (30.78)	139.96 (28.58)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and Fluctuation parameters are expressed as the arithmetic means (CV%) only.

Table 7:

Summary Table of the Comparative Bioavailability Study
of Morphine SR vs MS Contin®, Morphine Sulfate 60 mg tablets conducted under fasting conditions in 16 healthy adult male volunteers
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test[1] Morphine SR	Reference[2] MS Contin®	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng.h/mL)	142.00 146.30 (24.3)	152.07 154.34 (17.5)	92	(88-97)
AUC_I (ng.h/mL)	172.78 179.04 (26.6)	184.35 188.99 (22.7)	93	(89-100)
AUC_{0-12}	111.08 115.67 (28.4)	115.99 118.27 (20.5)	95	(88-102)
C_{MAX} (ng/mL)	21.66 23.01 (33.6)	20.60 21.45 (32.0)	104	(96-112)
T_{MAX}[3] (h)	2.27 (44.6)	2.13 (50.1)	---	---
$T_{½}$[3] (h)	10.92 (46.1)	10.27 (43.7)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and T1/2 parameters are expressed as the arithmetic means (CV%) only.

Table 8:

Summary Table of the Comparative Bioavailability Study
of Morphine SR vs MS Contin®, Morphine Sulfate 60 mg tablets conducted under fed conditions in 20 healthy adult male volunteers
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	**Test**[1] Morphine SR	**Reference**[2] MS Contin®	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (ng.h/mL)	143.45 146.58 (22.0)	150.07 152.38 (18.2)	96	(90-102)
AUC_I (ng.h/mL)	166.19 169.66 (21.0)	176.20 178.51 (16.4)	94	(88-101)
AUC_{0-12}	115.52 118.58 (24.8)	120.86 123.41 (21.3)	96	(89-103)
C_{MAX} (ng/mL)	21.91 23.91 (52.0)	22.20 23.89 (43.3)	99	(82-119)
T_{MAX}[3] (h)	3.25 (38.4)	3.33 (38.1)	---	---
$T_{½}$[3] (h)	9.53 (29.7)	10.09 (32.4)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The Tmax and T1/2 parameters are expressed as the arithmetic means (CV%) only.

Table 9:

Summary Table of the Comparative Bioavailability Study
of Morphine SR vs MS Contin®, Morphine Sulfate 60 mg tablets conducted under steady-state conditions in 24 healthy adult male volunteers
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test[1] Morphine SR	Reference[2] MS Contin®	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_{λ} (ng.h/mL)	254.22 261.03 (23.2)	270.06 274.74 (20.0)	94	(91-98)
C_{MAX} (ng/mL)	33.83 34.90 (25.8)	35.63 36.25 (20.3)	95	(90-101)
C_{MIN} (ng/mL)	10.22 10.76 (31.9)	10.57 11.08 (31.6)	97	(91-103)
T_{MAX}[3] (h)	2.26 (44.3)	2.12 (72.6)	---	---
Fluctuation[3] (%)	111.33 (21.3)	111.4 (24.8)	---	---

1 Morphine SR tablets manufactured for Sandoz Canada Inc.
2 MS Contin® is manufactured by Purdue Frederick and was purchased in Canada.
3 The T_{max} and Fluctuation parameters are expressed as the arithmetic means (CV%) only.

Conclusion: In each single-dose study, the 90% confidence intervals for the ln-transformed parameters AUC_t, AUC_{inf}, AUC_{0-12} and C_{max} for morphine were within the 80-125% TPD acceptance range both before and after correction for measured content. Similarly in the steady-state studies conducted, the 90% geometric confidence interval for AUC_{λ} and the ratio of means for C_{max} and C_{min} were within the 80-125% TPD acceptance range both before and after correction for measured content. Based on these results, Morphine SR and MS Contin® (morphine sulfate) 15, 30 and 60 mg tablets are considered bioequivalent under single-dose fasting, fed and steadystate conditions.

A randomized, blinded, single dose, 2-way crossover comparative bioavailability study was conducted in fasting condition on 24 healthy adults (20 males and 4 females) subjects. The bioavailability of Sandoz Morphine SR sustained-release tablets, 200 mg, relative to MS Contin® sustained-release tablets, 200 mg was determined following single 1 x 200 mg doses. The average values of the pharmacokinetic parameters as well as ratio of means (with 90% confidence intervals) are listed in the following tables.

Table 10: SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Morphine Sulfate (1 x 200 mg) From measured data Geometric LS Mean Arithmetic Mean (CV %)				
Parameter	**Test**[1] Morphine SR	**Reference**[2] MS Contin®	% Ratio of Geometric LS Means	90% Confidence Interval
AUC_T (ng·h/mL)	892.059 909.953 (20.9%)	935.157 955.486 (21.5%)	95.4	91.2 - 99.8
AUC_∞ (ng·h/mL)	900.071 915.101 (19.2%)	957.114 977.805 (21.5%)	94.0	89.7 - 98.6
C_{max} (ng/mL)	82.950 89.065 (40.3%)	72.793 77.084 (37.0%)	114.0	101.6 - 127.8
T_{max}[§] (h)	5.00 (1.33-6.00)	5.00 (0.67-6.00)		
$T_{½}$[€] (h)	11.80 (37.4)	12.65 (37.6)		

[*] Morphine SR 200 mg tablets manufactured for Sandoz Canada Inc
[†] MS Contin® (morphine sulfate) 200 mg sustained-release tablet, Purdue Pharma, Canada
[§] Expressed as the median (range) only
[€] Expressed as the arithmetic mean (CV%) only

A randomized, blinded, single dose, 2-way crossover comparative bioavailability study was conducted in fed condition on 28 healthy adults (20 males and 8 females) subjects. The bioavailability of Sandoz Morphine SR sustained-release tablets, 200 mg, relative to MS Contin® sustained-release tablets, 200 mg was determined following single 1 x 200 mg doses. The average values of the pharmacokinetic parameters as well as ratio of means (with 90% confidence intervals) are listed in the following tables.

Table 11: SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Morphine Sulfate (1 x 200 mg) From measured data Geometric LS Mean Arithmetic Mean (CV %)				
Parameter	**Test**[1] Morphine SR	**Reference**[2] MS Contin®	% Ratio of Geometric LS Means	90% Confidence Interval
AUC_T (ng·h/mL)	991.809 1004.501 (30.3%)	1051.749 1075.287 (30.5%)	94.3	88.6 - 100.4
AUC_∞ (ng·h/mL)	1015.332 1028.802 (30.4%)	1072.590 1096.559 (30.1%)	94.7	88.8 - 100.9
C_{max} (ng/mL)	109.244 112.061 (34.3%)	122.794 138.172 (43.2%)	89.0	74.6 - 106.1
T_{max}[§] (h)	5.00 (1.50-8.00)	3.67 (1.50-8.00)		
$T_{½}$[€] (h)	12.11 (34.0)	11.15 (26.8)		

[*] Morphine Sulfate 200 mg sustained-release tablet, Sandoz Canada
[†] MS Contin® (morphine sulfate) 200 mg sustained-release tablet, Purdue Pharma, Canada
[§] Expressed as the median (range) only
[€] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

- Animal

Table 12 – Morphine lethal dose toxicity values in animals

Acute:	**Oral LD_{50}**
Mice	650 mg/kg
Rats	460 mg/kg
Guinea Pigs	1000 mg/kg

Morphine toxicity varies considerably from species to species. In some species, relatively low doses of morphine cause hypothermia and gross excitation. In the rat, for example, doses suitable for analgesia also affect a continually restless and seemingly frightened state. These effects are antagonized by naloxone and are prevented by phenytoin.

- Human

Morphine toxicity may result from overdosage but because of the great inter-individual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal.

The presence of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggests that in a morphine naive, pain-free individual, the lethal oral dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity.

17 SUPPORTING PRODUCT MONOGRAPHS

MS CONTIN® (Tablets, 15 mg, 30 mg, 60 mg, 100 mg and 200 mg), submission control 259272, Product Monograph, Purdue Pharma. (July 4, 2022).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]Sandoz Morphine SR

Morphine Sulfate Sustained Release Tablets

Read this carefully before you start taking Sandoz Morphine SR tablets and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Sandoz Morphine SR.

Serious Warnings and Precautions

- Even if you take Sandoz Morphine SR as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).

- When you take Sandoz Morphone SR it must be swallowed whole. Do not break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.

- Life-threatening breathing problems can happen while taking Sandoz Morphine SR, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.

- Never give anyone your Sandoz Morphine SR. They could die from taking it. If a person has not been prescribed Sandoz Morphine SR, taking even one dose can cause a fatal overdose. This is especially true for children.

- If you took Sandoz Morphine SR while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery.
  If your baby has any of the following symptoms:
  - has changes in their breathing (such as weak, difficult or fast breathing)
  - is unusually difficult to comfort
  - has tremors (shakiness)
  - has increased stools, sneezing, yawning, vomiting, or fever
  - Seek immediate medical help for your baby.

- Taking Sandoz Morphine SR with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

What is Sandoz Morphine SR used for?
Sandoz Morphine SR is used in adults and children (less than 18 years of age) to manage long-term pain, when:

- the pain is severe enough to require daily, around-the-clock pain medication; and

- the healthcare professional determines that other treatment options are not able to effectively manage your pain

It is NOT used “as needed” to treat pain that you only have once in a while.

How does Sandoz Morphine SR work?
Sandoz Morphine SR is painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Sandoz Morphine SR?

Medicinal ingredients: morphine sulfate

Non-medicinal ingredients: hypromellose, lactose anhydrous, magnesium stearate, polyethylene glycol, polyvinyl alcohol, stearic acid, talc and titanium dioxide.

The tablet coatings contain the following additional ingredients:

- 15 mg: FD&C blue #1 brilliant blue FCF aluminum lake
  FD&C yellow #5 tartrazine aluminum lake

- 30 mg: D&C red #7 lithol rubin B calcium lake
  FD&C blue #1 brilliant blue FCF aluminum lake

- 60 mg: FD&C yellow #6 sunset yellow FCF aluminum lake

- 100 mg: FD&C Blue #2/ Indigo Carmine AL 3%-5%
  Ferrosoferric oxide/black iron oxide
  Iron Oxide Yellow

- 200 mg: Erythrosine Aluminum Lake
  FD&C Blue #2/ Indigo Carmine Aluminum Lake
  FD&C Yellow #6/ Sunset Yellow FCF Aluminum Lake

Sandoz Morphine SR comes in the following dosage forms:

Sustained Release Tablets: 15 mg, 30 mg, 60 mg, 100 mg and 200 mg of morphine sulfate.

Do not use Sandoz Morphine SR if:
- your healthcare professional did not prescribe it for you.
- you are allergic to morphine, or any of the other ingredients of Sandoz Morphine SR.
- you have mild or short term pain that can be controlled by the occasional use of painkillers, including those available without a prescription.
- you have severe asthma, trouble breathing or other lung problems.
- you have any heart problems.
- you have bowel blockage or narrowing of the stomach or intestines.
- you have a condition where the bowel does not work properly (ileus), or you have severe pain in your abdomen.
- you have increased pressure in your skull, have a head injury or a brain tumour.
- you have severe CNS depression (nervous system slows down).
- you are at risk for seizures.

- you have a history with epilepsy.
- you suffer from alcoholism or alcohol withdrawal.
- you are taking or have taken within the past 2 weeks a monoamine oxidase inhibitor (MAOI) medication (such as phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegiline).
- you are pregnant or plan to become pregnant, or are in labour and delivery.
- you are breast-feeding.
- you are going to have a surgery or operation, or have had a surgery in the last 24 hours.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Sandoz Morphine SR. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse.
- have kidney or liver problems.
- have sickle cell disease.
- have been told you are at risk of having heart problems or seizures.
- have a history of sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).have low blood pressure.
- have past or current depression.
- suffer from chronic or severe constipation.
- have problems with your thyroid, adrenal or prostate gland.
- have, or have had in the past,problems with your mood (such as depression or anxiety), hallucinations, or other severe mental health problems..
- have gastrointestinal (GI) problems.
- are planning to become breastfeed.
- have difficulty urinating.
- are over 50 years of age.
- have a condition that causes weakness or frailty.
- have circulatory problems (e.g. body does not get enough oxygen and nutrients to function properly due to lack of blood flow).
- are planning on drinking alcohol. Drinking alcohol while taking Sandoz Morphine SR may cause dangerous side effects, including death. Do not drink alcohol while taking Sandoz Morphine SR.
- take hypnotics, centrally acting analgesics, opioids, or psychotropic medicines. Ask your healthcare professional if you are unsure.

Other warnings you should know about:

Taking Sandoz Morphine SR can cause the following serious side effects:

- **Disorder of the adrenal gland:** You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:
    - nausea, vomiting;
    - feeling tired, weak or dizzy;
    - decreased appetite.

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your healthcare professional may do tests, give you another medication, and slowly take you off Sandoz Morphine SR.

- **Serotonin toxicity (also known as serotonin syndrome**): Sandoz Morphine SR can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take Sandoz Morphine SR with certain anti-depressants or migraine medications. Serotonin toxicity symptoms include:
    - fever, sweating, shivering, diarrhea, nausea, vomiting;
    - muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
    - fast heartbeat, changes in blood pressure;
    - confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

- **Sleep apnea:** Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your healthcare professionalif you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Do not use Sandoz Morphine SR while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. Sandoz Morphine SR can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking Sandoz Morphine SR, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your healthcare professional will monitor and guide you on how to slowly stop taking Sandoz Morphine SR. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Sandoz Morphine SR. Sandoz Morphine SR can cause:
- drowsiness,
- dizziness, or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

Sexual Function and Reproduction
Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Worsening Pain:
Taking opioids for pain can causesometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell healthcare professional if you notice a change like this in your pain while you are taking Sandoz Morphine SR.

Testing and check-ups:

Your healthcare professional will regularly monitor your health. This includes monitoring for signs of:

- misuse and abuse;
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping);
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Serious drug interactions with Sandoz Morphine SR include:

- benzodiazepines used to help you sleep or that help reduce anxiety.
- central nervous system (CNS) depressants used to slow down the nervous system. These can include:
  - other opioids and mixed opioid agonists/antagonists used to relieve pain (e.g., methadone, pentazocine, nalbuphine, butorphanol, buprenorphine);
  - hypnotics used to help with sleeping;
  - antidepressants used for depression and mood disorders (e.g., fluoxetine, citalopram, venlafaxine; tricyclic antidepressants such as amitriptyline, imipramine, maprotiline, paroxetine; serotonin norepinephrine re-uptake inhibitors [SNRIs]; and selective serotonin re-uptake inhibitors [SSRIs] such as St. John's Wort);
  - anxiolytics, tranquilizers, and phenothiazines used to treat mental or emotional disorders;
  - muscle relaxants used to treat muscle spasms and back pain (e.g., baclofen);
  - general anaesthetics used during surgery;
  - antipsychotics and neuroleptics used to treat mental health disorders (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, and risperidone);
  - antihistamines used to treat allergies;
  - antiemetics used to prevent nausea or vomiting (e.g., domperidone, granisetron, dolasetron, and ondansetron);
  - sedatives which may enhance the drowsiness;
  - pregabalin, used to treat nerve pain;
  - gabapentin, used to prevent and control seizures in the treatment of epilepsy;
  - beta blockers used to lower blood pressure;
  - alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking Sandoz Morphine SR. It can lead to drowsiness, usually slow or weak breathing, serious side effects, or a fatal overdose.
- monoamine oxidase inhibitors (MAOIs) used to treat depression. Do not take Sandoz Morphine SR with MAOIs or if you have taken MAOIs in the last 14 days.

The following may also interact with Sandoz Morphine SR:

- anticoagulants, used to thin the blood and prevent blood clots (e.g., warfarin and other coumarins)
- drugs used to treat migraines (e.g. triptans)

If you are unsure about the medications you are taking, ask your healthcare professional.

How to take Sandoz Morphine SR:

- Sandoz Morphine SR must be taken orally, by mouth. Do **NOT** administer the Sandoz Morphine SR tablets via any other route as this can cause serious harm, including death.
- Take Sandoz Morphine SR every 12 hours as prescribed, with a glass of water. It can be taken with or without food.
- **Swallow the whole tablet. Do not cut, break, chew, dissolve or crush Sandoz Morphine SR tablets. This can be dangerous and can lead to death or seriously harm you. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.**
- The Sandoz Morphine SR 100 mg and 200 mg strength tablets will only be prescribed if you are "opioid tolerant". Your healthcare professional will tell you when you are "opioid tolerant" to a certain dose of Sandoz Morphine SR.
- Review your pain regularly with your healthcare professional to determine if you still need Sandoz Morphine SR. Be sure to use Sandoz Morphine SR only for the condition for which it was prescribed.

Usual dose:

Your dose is tailored/personalized just for you. Take it exactly as your healthcare professional has told you to. Do not increase or decrease your dose without consulting your healthcare professional. Taking higher doses can lead to more side effects and a greater chance of overdose.

Stopping Your Medication

If you have been taking Sandoz Morphine SR for more than a few days you should not stop taking it all of a sudden. Your healthcare professional will monitor and guide you on how to slowly stop taking Sandoz Morphine SR. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If

you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking Sandoz Morphine SR.

Refilling Prescriptions for Sandoz Morphine SR:

A new written prescription is required from your healthcare professional each time you need more Sandoz Morphine SR. Therefore, it is important that you contact your healthcare professional before your current supply runs out.

Only obtain prescriptions for this medicine from the healthcare professional in charge of your treatment. Do not seek prescriptions from other healthcare professionals unless you switch to another healthcare professional for your pain management.

Overdose:

Signs of overdose with Sandoz Morphine SR may include:

- abnormally slow or weak breathing
- dizziness
- confusion
- extreme drowsiness
- shrinking or widening of the pupils
- floppy muscles/low muscle tone
- cold and clammy skin
- slow heart rate
- low blood pressure
- muscle weakness, cramping, or aching
- toxic leukoencephalopathy (a brain disorder affecting the brain's white matter)
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping)
- cardiac arrest (heart stops beating suddenly)

If you think you, or a person you are caring for, have taken too much Sandoz Morphine SR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you do not miss any doses. If you miss:

- **One dose:** Skip the missed dose and take your next dose as scheduled. Do not take two doses at once to make-up for a missed dose.
- **Several doses in a row:** Talk to your healthcare professional before restarting your medication.

What are possible side effects from using Sandoz Morphine SR?

These are not all the possible side effects you may have when taking Sandoz Morphine SR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- drowsiness
- insomnia
- dizziness
- fainting

- nausea, vomiting, or a poor appetite
- dry mouth
- headache
- problems with vision
- weakness, uncoordinated muscle movement
- itching
- sweating
- constipation. Talk with your healthcare professional about ways to prevent constipation when you start taking Sandoz Morphine SR.
- low sex drive, impotence (erectile dysfunction), infertility

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Hallucinations: seeing or hearing things that are not there.			√
Seizures (fits): uncontrollable shaking with or without loss of consciousness.			√
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory Depression: Slow, shallow or weak breathing.			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness.	√		
Serotonin toxicity (also known as serotonin syndrome): a reaction which may cause feelings of agitation or restlessness, flushing, muscle			√

twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles.			
UNKNOWN FREQUENCY			
Disorder of the adrenal gland: nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure.			√
Sleep apnea: stop breathing for short periods during your normal nightly sleep.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep Sandoz Morphine SR in a cool, dry place, between 15 and 30°C. Protect from light. Protected from moisture.
- Keep unused or expired Sandoz Morphine SR in a secure place to prevent theft, misuse or accidental exposure.
- Keep Sandoz Morphine SR under lock, out of sight and reach of children and pets.
- Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Sandoz Morphine SR, get emergency help right away.
- Sandoz Morphine SR should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about Sandoz Morphine SR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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