PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[N]TEVA-MORPHINE SR

Morphine Sulfate Sustained Release Tablets
Tablets, 15 mg, 30 mg, 60 mg, 100 mg and 200 mg, Oral
Teva Standard
Opioid Analgesic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9
www.tevacanada.com

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, General, Addiction, Abuse and Misuse	06/2024
7 WARNINGS AND PRECAUTIONS, Neurologic, Opioid-induced hyperalgesia	06/2024
7 WARNINGS AND PRECAUTIONS, Respiratory, Acute Chest Syndrome (ACS) in Patients with Sickle Cell Disease	06/2024
7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Hepatic/Biliary/Pancreatic	06/2024

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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

TEVA-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

TEVA-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 morphine sulfate sustained release tablets 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, Geriatrics).

2 CONTRAINDICATIONS

TEVA-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 tumour 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, TEVA-MORPHINE SR 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

  TEVA-MORPHINE SR poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing TEVA-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). TEVA-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 TEVA-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 TEVA-MORPHINE SR or following a dose increase (7 WARNINGS AND PRECAUTIONS, Respiratory, Respiratory Depression).

  TEVA-MORPHINE SR 15, 30, 60 and 100 mg tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving TEVA-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 TEVA-MORPHINE, 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 TEVA-MORPHINE SR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (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 TEVA-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 TEVA-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 TEVA-MORPHINE SR not be exceeded. Each patient should be assessed for their risk prior to prescribing TEVA-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 TEVA-MORPHINE SR (see 4.2 Recommended Dose and Dosage Adjustment).**

- **TEVA-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.**

- **TEVA-MORPHINE SR 15, 30, 60 and 100 mg tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving TEVA-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.

- TEVA-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).

- TEVA-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 TEVA-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 TEVA-MORPHINE SR Treatment

  The usual initial adult dose of TEVA-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 TEVA-MORPHINE SR at the same total daily morphine dosage, equally divided into two 12 hourly TEVA-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 TEVA-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. TEVA-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 (TEVA-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 TEVA-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 TEVA-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.

TEVA-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 (TEVA-MORPHINE SR). However, where judged necessary for optimization of drug effects, TEVA-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 TEVA-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 TEVA-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. TEVA-MORPHINE SR is a sustained release formulation and therefore is not intended for use as rescue medication.

4.4 Administration

TEVA-MORPHINE SR sustained release tablets may be taken with or without food, with a glass of water.

4.5 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, skeletal muscle flaccidity, 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 mg, 30 mg, 60 mg, 100 mg and 200 mg	Tablet core (all strengths): Colloidal Silicon Dioxide, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate and Stearic Acid. Tablet Coating: Polyvinyl Alcohol (Partially Hydrolyzed), Polyethylene Glycol 3350, Talc, Titanium Dioxide Additional coating ingredients specific to each strength: 15 mg: D&C Yellow No.10 Aluminum Lake, FD&C Blue No.1 Aluminum Lake, FD&C Red No.40 Aluminum Lake 30 mg: FD&C Blue No.2 Aluminum Lake, D&C Red No.27 Aluminum Lake, FD&C Yellow No.6 Aluminum Lake 60 mg: FD&C Yellow No.6 Aluminum Lake, FD&C Red No.40 Aluminum Lake

		100 mg: FD&C Blue No.2 Aluminum Lake, FD&C Yellow No.6 Aluminum Lake, FD&C Red No.40 Aluminum Lake 200 mg: D&C Red No.30 Aluminum Lake, FD&C Red No.40 Aluminum Lake

- Dosage Forms

  15 mg: Green, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 15 on the other side.

  30 mg: Violet, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 30 on the other side.

  60 mg: Orange, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 60 on the other side.

  100 mg: Grey, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 100 on the other side.

  200 mg: Red, scored, caplet-shaped, sustained release, film-coated, biconvex tablets, engraved N scoreline N on one side and 200 on the other side.

- Packaging

  TEVA-MORPHINE SR 15 mg tablets are supplied in bottles of 50 tablets.

  TEVA-MORPHINE SR 30 mg, 60 mg, 100 mg and 200 mg tablets are supplied in bottles of 50 and 100 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 TEVA-MORPHINE SR to anyone other than for whom it was prescribed, as such, inappropriate use may have severe medical consequences, including death. TEVA-MORPHINE SR should be stored securely to avoid theft or misuse.

TEVA-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.

TEVA-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 TEVA-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 sulfate may occur in particular in high doses. A morphine sulfate dose reduction or change in opioid may be required.

- Addiction, Abuse and Misuse

Like all opioids, TEVA-MORPHINE SR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, TEVA-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 TEVA-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.

TEVA-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 TEVA-MORPHINE SR is dispensed to them. Patients receiving TEVA-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 TEVA-MORPHINE SR contains morphine, an opioid pain medicine.
3. Patients should be advised that TEVA-MORPHINE SR should only be taken as directed. The dose of TEVA-MORPHINE SR should not be adjusted without consulting with a physician. TEVA-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 TEVA-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 TEVA-MORPHINE SR.
7. Patients should be advised that if they have been receiving treatment with TEVA-MORPHINE SR and cessation of therapy is indicated, it may be appropriate to taper the TEVA-MORPHINE SR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.
8. Patients should be informed that TEVA-MORPHINE SR could cause seizures if they are at risk for seizure or have epilepsy. Patients should be advised not to take TEVA-MORPHINE SR if they have seizure disorders. Patients should be advised to stop taking TEVA-MORPHINE SR if they have a seizure while taking TEVA-MORPHINE SR and seek medical help immediately.
9. Patients should be advised of the most common adverse reactions that may occur while taking TEVA-MORPHINE SR: constipation, dizziness, hyperhidrosis, nausea, sedation and vomiting. If symptoms worsen, seek immediate medical attention.
10. Patients should be advised that TEVA-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 TEVA-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 TEVA-MORPHINE SR.
11. Patients should be advised that TEVA-MORPHINE SR is a potential drug of abuse. They should protect it from theft or misuse.
12. Patients should be advised that TEVA-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 TEVA-MORPHINE SR. Women who are breast-feeding or pregnant should not use TEVA-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 TEVA-MORPHINE SR.

The use of TEVA-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 and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of TEVA-MORPHINE SR and there is a potential for development of psychological dependence. TEVA-MORPHINE SR should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential.

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.

> Abuse or intentional misuse of TEVA-MORPHINE SR may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).
>
> Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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, gooseflesh, 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 Dose 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

  TEVA-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 TEVA-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 TEVA-MORPHINE SR tablets. The clinical significance of these findings is unknown.

Driving and Operating Machinery

TEVA-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 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. (see 2 CONTRAINDICATIONS, 8.1 Adverse Reaction Overview, Nausea and Vomiting, and 8.1 Adverse Reaction Overview ,Constipation).

Hepatic/Biliary/Pancreatic

Morphine can cause spasm of the sphincter of Oddi and an increase in intrabiliary pressure. Other opioid related effects may include a reduction in biliary and pancreatic secretions or elevations in serum amylase. Morphine should be avoided in patients with biliary tract disorders. Monitor patients for worsening symptoms related to biliary tract disease, including acute pancreatitis. (see 2 CONTRAINDICATIONS).

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, gabapentinoids, baclofen 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. TEVA-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 TEVA-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).

TEVA-MORPHINE SR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 CONTRAINDICATIONS, 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 TEVA-MORPHINE SR may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, TEVA-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 morphine sulfate sustained release tablets, 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 TEVA-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

TEVA-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 TEVA-MORPHINE SR for at least 24 hours before the operation and TEVA-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 TEVA-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 TEVA-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 (CO2) 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 TEVA-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 TEVA-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 TEVA-MORPHINE SR are essential. Overestimating the TEVA-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).

TEVA-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 TEVA-MORPHINE SR, as in these patients, even usual therapeutic doses of TEVA-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 TEVA-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

Morphine 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, TEVA-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, TEVA-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 TEVA-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 TEVA-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).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects of TEVA-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 (≥ 1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

- 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, sphincter of Oddi dysfunction

- 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 TEVA-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. TEVA-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). TEVA-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. TEVA-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 TEVA-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, such as morphine sulfate, 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 spasm of the sphincter of Oddi.

- 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 TEVA-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

  TEVA-MORPHINE SR 15 mg tablets: store tablets at room temperature (15°C - 25°C).
  Protect from light.

TEVA-MORPHINE SR 30 mg, 60 mg, 100 mg and 200 mg tablets: Store tablets at room temperature (15°C - 30°C). Protect from light.

- Disposal

  TEVA-MORPHINE SR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired TEVA-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. TEVA-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

TEVA-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. TEVA-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

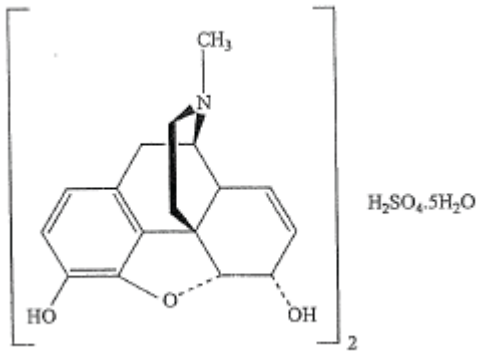
Proper name: morphine sulfate

Chemical name: (5α,6α) 7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol sulphate (2:1 salt) pentahydrate
di[(5R,6S)-4,5-epoxy-N-methylmorphin-7-ene-3,6-diol]sulphate pentahydrate

Molecular formula: $(C_{17}H_{19}NO_3)_2\,H_2SO_4 \bullet 5H_2O$

Molecular mass: 758.8 (pentahydrate) g/mol
668.8 (anhydrous) g/mol

Structural Formula:



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

Product Characteristics:

- Physical Description:

  White or almost white crystalline powder.

- 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.

14.2 Comparative Bioavailability Studies

A randomized, two period, 2-way crossover, single-dose bioavailability study was conducted in healthy adult male and female subjects. The bioavailability of Teva-Morphine SR (sustained-release) 15 mg tablets (Teva Canada Limited, Canada) relative to MS Contin® 15 mg sustained-release tablets (Purdue Pharma, Canada) was determined following single 1 x 15 mg dose under fed conditions.

Comparative bioavailability data from 34 subjects who were included in the statistical analysis are summarized in the table below.

Morphine (1x 15 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng*h/mL)	53.28 55.07 (27)	52.96 54.64 (25)	100.6	96.8 - 104.6
AUC_I (ng*h/mL)	60.32 61.35 (26)	58.69 60.12 (22)	102.8	99.4 - 106.3
C_{max} (ng/mL)	8.11 8.40 (25)	8.78 9.22 (33)	92.3	85.0 - 100.2
T_{max}[3] (h)	2.79 (48)	2.72 (46)		
$T_{½}$[3] (h)	12.17 (35)	13.05 (32)		

[1] Teva-Morphine SR Tablets 15 mg (Teva Canada Limited, Canada)
[2] MS Contin® 15 mg Sustained Release Tablets (Purdue Pharma, Canada).
[3] Expressed as the arithmetic mean (CV %) only

A randomized, two period, 2-way crossover, single-dose bioavailability study was conducted in healthy adult male and female subjects. The bioavailability of Teva-Morphine SR (sustained-release) 15 mg tablets (Teva Canada Limited, Canada) relative to MS Contin® 15 mg sustained-release tablets (Purdue Pharma, Canada) was determined following single 1 x 15 mg dose under fasting conditions.

Comparative bioavailability data from 22 subjects who were included in the statistical analysis are summarized in the table below.

Morphine (1 x 15 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_t (ng∗h/mL)	52.67 54.63 (27)	53.37 55.50 (27)	98.7	95.1 – 102.4
AUC_{inf} (ng∗h/mL)	58.85 62.26 (22)	59.88 61.01 (25)	98.3	94.5 – 102.2
C_{max} (ng/mL)	6.30 6.52 (27)	6.80 7.05 (26)	92.6	87.6 – 97.9
T_{max}[§] (h)	1.75 (55)	1.74 (72)		
$T_{½}$[§] (h)	10.78 (68)	11.19 (42)		

[1] Teva-Morphine SR Tablets 15 mg (Teva Canada Limited, Canada)
[2] MS Contin® 15 mg Sustained Release Tablets (Purdue Pharma, Canada).
[3] Expressed as the arithmetic mean (CV %) only

A randomized, two period, 2-way crossover, multiple-dose bioavailability study was conducted in healthy adult male and female subjects. The bioavailability of Teva-Morphine SR (sustained-release) 15 mg tablets (Teva Canada Limited, Canada) relative to MS Contin® 15 mg sustained-release tablets (Purdue Pharma, Canada) was determined following multiple-dose 1 x 15 mg (q12h), under fasting conditions.

Comparative bioavailability data from 20 subjects who were included in the statistical analysis are summarized in the table below.

Morphine (1 x 15 mg, q12h) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{tau} (ng∗h/mL)	61.64 63.16 (23)	62.06 63.69 (24)	99.3	94.6 - 104.3
C_{max} (ng/mL)	8.63 8.80 (20)	9.35 9.60 (24)	92.3	87.6 – 97.4
C_{min} (ng/mL)	2.48 2.60 (35)	2.32 2.49 (38)	106.9	93.0 – 122.7
T_{max}[3] (h)	2.30 (57)	1.98 (58)		
FL[3] (%)	119.88 (19)	135.45 (22)		

[1] Teva-Morphine SR Tablets 15 mg (Teva Canada Limited, Canada)

[2] MS Contin® 15 mg Sustained Release Tablets (Purdue Pharma, Canada).

[3] Expressed as the arithmetic mean (CV %) only

A randomized, two period, 2-way crossover, single-dose bioavailability study was conducted in healthy adult male and female subjects. The bioavailability of Teva-Morphine SR (sustained-release) 200 mg tablets (Teva Canada Limited, Canada) relative to MS Contin® 200 mg sustained-release tablets (Purdue Pharma, Canada) was determined following single 1 x 200 mg dose under fed conditions.

Comparative bioavailability data from 28 subjects who were included in the statistical analysis are summarized in the table below.

Morphine (1x 200 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng∗h/mL)	957.66 1023.93 (44)	962.00 1017.23 (43)	99.6	96.5 - 102.7
AUC_I (ng∗h/mL)	1012.94 1082.01 (45)	1024.0 1083.68 (45)	98.9	95.8 - 102.2
C_{max} (ng/mL)	106.75 113.30 (37)	108.11 115.11 (38)	98.7	89.5 - 108.9
T_{max}[3] (h)	4.07 (37)	3.82 (65)		
$T_{½}$[3] (h)	10.15 (28)	11.46 (28)		

[1] Teva-Morphine SR Tablets 200 mg (Teva Canada Limited, Canada)
[2] MS Contin® 200 mg Sustained Release Tablets (Purdue Pharma, Canada).
[3] Expressed as the arithmetic mean (CV %) only

A randomized, two period, 2-way crossover, single-dose bioavailability study was conducted in healthy adult male and female subjects. The bioavailability of Teva-Morphine SR (sustained-release) 200 mg tablets (Teva Canada Limited, Canada) relative to MS Contin® 200 mg sustained-release tablets (Purdue Pharma, Canada) was determined following single 1 x 200 mg dose under fasting conditions.

Comparative bioavailability data from 19 subjects who were included in the statistical analysis are summarized in the table below.

Morphine (1 x 200 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng*h/mL)	878.02 901.99 (23)	813.66 843.04 (25)	107.9	99.9 – 116.6
AUC_I (ng*h/mL)	910.64 936.03 (23)	845.63 878.55 (26)	107.7	99.2 – 116.9
C_{max} (ng/mL)	84.96 90.45 (34)	69.90 75.13 (36)	121.5	112.6 – 131.2
T_{max}[3] (h)	2.91 (33)	2.64 (44)		
$T_{½}$[3] (h)	9.70 (22)	9.97 (24)		

[1] Teva-Morphine SR Tablets 200 mg (Teva Canada Limited, Canada)

[2] MS Contin® 200 mg Sustained Release Tablets (Purdue Pharma, Canada).

[3] Expressed as the arithmetic mean (CV %) only

A randomized, two period, 2-way crossover, multiple-dose bioavailability study was conducted in healthy adult male and female subjects. The bioavailability of Teva-Morphine SR (sustained-release) 200 mg tablets (Teva Canada Limited, Canada) relative to MS Contin® 200 mg sustained-release tablets (Purdue Pharma, Canada) was determined following multiple-dose 1 x 200 mg (q12h), under fasting conditions.

Comparative bioavailability data from 23 subjects who were included in the statistical analysis are summarized in the table below.

Morphine (1 x 200 mg, q12h) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{tau} (ng∗h/mL)	1232.49 1290.28 (30)	1086.10 1148.68 (34)	113.5	105.6 – 122.0
C_{max} (ng/mL)	160.35 169.75 (34)	137.24 144.07 (34)	116.8	110.1 - 124.1
C_{min} (ng/mL)	57.09 60.33 (33)	47.99 54.16 (45)	119.0	105.3 - 134.4
T_{max}[§] (h)	3.70 (24)	3.39 (44)		
FL[§](%)	101.02 (25)	98.63 (37)		

[1] Teva-Morphine SR Tablets 200 mg (Teva Canada Limited, Canada)
[2] MS Contin® 200 mg Sustained Release Tablets (Purdue Pharma, Canada).
[3] 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 3 – Morphine lethal dose toxicity values in animals

Acute	**Oral LD50**
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

1. MS CONTIN® (Tablets; 15 mg, 30 mg, 60 mg, 100 mg and 200 mg), submission control # 273271, Product Monograph, Purdue Pharma. (August 14, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{N}TEVA-MORPHINE SR

Morphine Sulfate Sustained Release Tablets

Read this carefully before you start taking **TEVA-MORPHINE SR** 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 **TEVA-MORPHINE SR**.

Serious Warnings and Precautions

- Even if you take TEVA-MORPHINE SR as prescribed you are at risk for opioid addiction, abuse, and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your healthcare professional.
- When you take TEVA-MORPHINE 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 TEVA-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 TEVA-MORPHINE SR. They could die from taking it. If a person has not been prescribed TEVA-MORPHINE SR, taking even one dose can cause a fatal overdose. This is especially true for children.
- If you took TEVA-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 TEVA-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 TEVA-MORPHINE SR used for?

TEVA-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 TEVA-MORPHINE SR work?

TEVA-MORPHINE SR is a 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 TEVA-MORPHINE SR?

Medicinal ingredient: morphine sulfate

Non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), polyethylene glycol 3350, stearic acid, talc and titanium dioxide.

The tablet coatings contain the following additional ingredients:

- 15 mg: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake

- 30 mg: FD&C Blue No. 2 Aluminum Lake, D&C Red No. 27 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake

- 60 mg: FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake

- 100 mg: FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, FD&C Red No. 40 Aluminum Lake

- 200 mg: D&C Red No. 30 Aluminum Lake, FD&C Red No. 40 Aluminum Lake

TEVA-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 TEVA-MORPHINE SR if:

- your healthcare professional did not prescribe it for you.
- you are allergic to morphine, or any of the other ingredients of TEVA-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).
- you have severe pain in your abdomen (for example, from appendicitis or pancreatitis).
- 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 have or 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) (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 TEVA-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 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 problems with your mood (such as depression or anxiety), hallucinations, or other mental health problems.
- have gastrointestinal (GI) problems.
- have a history of pancreas or gall bladder problems.
- are planning to 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 TEVA-MORPHINE SR may cause dangerous side effects, including death. Do not drink alcohol while taking TEVA-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 TEVA-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 TEVA-MORPHINE SR.

- **Serotonin toxicity (also known as serotonin syndrome):** TEVA-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 TEVA-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: Like any opioid, TEVA-MORPHINE SR may cause mental and physical dependence. Morphine sulfate also has the potential to cause addiction. There are important differences between physical dependence and addiction. Tolerance means that, over time, a higher dose may be needed to get the same level of pain relief. It is important that you talk to your healthcare professional if you have questions or concerns about addiction, physical dependence, or tolerance.
Your healthcare professional should prescribe and administer TEVA-MORPHINE SR with the same degree of caution appropriate to the use of other oral opioid medications. It is not recommended to use these products for a long period of time.

Pregnancy, nursing, labour and delivery: Do not use TEVA-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. TEVA-MORPHINE SR can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking TEVA-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 TEVA-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 TEVA-MORPHINE SR. TEVA-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 sometimes 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 your healthcare professional if you notice a change like this in your pain while you are taking TEVA-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 TEVA-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 TEVA-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 TEVA-MORPHINE SR with MAOIs or if you have taken MAOIs in the last 14 days.

The following may also interact with TEVA-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 TEVA-MORPHINE SR:

- TEVA-MORPHINE SR must be taken orally, by mouth. Do **NOT** administer the TEVA-MORPHINE SR tablets via any other route as this can cause serious harm, including death.
- Take TEVA-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 TEVA-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 TEVA-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 TEVA-MORPHINE SR.
- Review your pain regularly with your healthcare professional to determine if you still need TEVA-MORPHINE SR. Be sure to use TEVA-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.

<u>Stopping Your Medication</u>

If you have been taking TEVA-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 TEVA-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 TEVA-MORPHINE SR.

Refilling Prescriptions for TEVA-MORPHINE SR:

A new written prescription is required from your healthcare professional each time you need more TEVA-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 TEVA-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 **TEVA-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 TEVA-MORPHINE SR?

These are not all the possible side effects you may have when taking TEVA-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 TEVA-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			

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**	
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			

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**	
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.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:

- TEVA-MORPHINE SR 15 mg tablets: store tablets at room temperature (15°C - 25°C). Protect from light.
- TEVA-MORPHINE SR 30, 60, 100 and 200 mg tablets: Store tablets at room temperature (15°C - 30°C). Protect from light.
- Keep unused or expired TEVA-MORPHINE SR in a secure place to prevent theft, misuse, or accidental exposure.
- Keep TEVA-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 TEVA-MORPHINE SR, get emergency help right away.

- TEVA-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 TEVA-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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9.

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