PRODUCT MONOGRAPH

[N]TEVA-MORPHINE SR

Morphine Sulfate Sustained Release Tablets
15 mg, 30 mg, 60 mg, 100 mg and 200 mg

Teva Standard

Opioid Analgesic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal 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 #10/Aluminum Lake FD&C Blue #1/Aluminum Lake FD&C Red #40/ Aluminum Lake 30 mg: FD&C Blue #2/ Aluminum Lake D&C Red #27/Aluminum Lake FD&C Yellow #6/Aluminum Lake 60 mg: FD&C Yellow #6/Aluminum Lake FD&C Red #40/Aluminum Lake 100 mg: FD&C Blue #2/Aluminum Lake FD&C Yellow #6/Aluminum Lake FD&C Red #40/Aluminum Lake 200 mg: D&C Red #30/Aluminum Lake FD&C Red #40/Aluminum Lake

INDICATIONS AND CLINICAL USE

Adults
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.

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, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).**

Pediatrics (< 18 years of age)

Individual dosing requirements vary considerably based on each patient's age, weight, severity of pain, medical and analgesic history (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics)**.

CONTRAINDICATIONS

TEVA-MORPHINE SR (morphine sulfate sustained release tablets) is contraindicated in:

- Patients who are hypersensitive to the active substance (morphine) or other opioid analgesics, or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- 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, chronicobstructive airway, and status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, 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 **SERIOUS WARNINGS AND PRECAUTIONS and WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Limitations of Use

Because 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® (morphine sulfate sustained release tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

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 WARNINGS AND PRECAUTIONS). 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.

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 (see WARNINGS AND PRECAUTIONS). 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 SR, especially by children, can result in a fatal overdose of morphine (see DOSAGE AND ADMINISTRATION, 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 (see WARNINGS AND PRECAUTIONS).

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 WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

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 WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **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.**

General

TEVA-MORPHINE SR (morphine sulfate sustained release tablets) 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 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 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.

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

Addiction, Abuse and Misuse

Like all opioids, **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. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

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.

Carcinogenesis and Mutagenesis
See **TOXICOLOGY** section.

Cardiovascular
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 or certain anaesthetics.

Dependence/Tolerance
As with other opioids, tolerance and physical dependence may develop upon repeated administration of **TEVA-MORPHINE SR** and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptaion 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.

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.

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** unless used under extreme caution and awareness.

Endocrine

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and

continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal Effects

Morphine (and other morphine-like opioids) has been shown to decrease bowel motility. Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS and ADVERSE REACTIONS, Nausea and Vomiting and Constipation**).

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 **CONTRAINDICATIONS**).

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol):

Morphine should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation or coma may result.

When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored. **TEVA-MORPHINE SR** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see **DRUG INTERACTIONS**).

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 **DRUG INTERACTIONS**). 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 **DRUG INTERACTIONS**).

TEVA-MORPHINE SR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation,** and **DRUG INTERACTIONS**).

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 **CONTRAINDICATIONS**).
Serotonin syndrome: TEVA-MORPHINE SR could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. **TEVA-MORPHINE SR** should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

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. Also, morphine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine must be used with extreme caution and only if it is judged essential.

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

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.

Psychomotor Impairment

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.

Respiratory

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

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of **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.

To reduce the risk of respiratory depression, proper dosing and titration of **TEVA-MORPHINE SR** are essential (see DOSAGE AND ADMINISTRATION). Overestimating **the TEVA-MORPHINE SR** dose when converting patients from another opioid product can result in a fatal overdose with the first dose.

TEVA-MORPHINE SR 100 mg and 200 mg tablets are for use in opioid tolerant patients only (see **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 **CONTRAINDICATIONS**).

Patient Counselling Information

A patient information sheet should be provided when **TEVA-MORPHINE SR** is dispensed to the patient.

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.

4. **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.

5. 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.

6. 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.

7. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with **TEVA-MORPHINE SR**.

8. 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.

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.

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 not to take **TEVA-MORPHINE SR** if they have seizure disorders.

12. Patients should be advised that **TEVA-MORPHINE SR** is a potential drug of abuse. They should protect it from theft or misuse.

13. Patients should be advised that **TEVA-MORPHINE SR** should never be given to anyone other than the individual for whom it was prescribed.

14. 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**.

Sexual Function/Reproduction

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

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.

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 **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 **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**).

Labour, Delivery and Nursing Mothers:
TEVA-MORPHINE SR is contraindicated during labour, delivery, pregnancy and in nursing mothers. Morphine sulfate can cross the placental barrier and is also excreted in breast milk. 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.

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.

Geriatrics (> *65* years of age): 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.

Patients over 50 years of age tend to require much lower doses of morphine than in the younger age group. Morphine should be administered with caution and in a reduced dosage to elderly or debilitated patients. The initial dose usually starts at the low end of the dosing range.

***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 morphine sulfate sustained release tablets. The clinical significance of these findings is unknown.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse effects of morphine sulfate sustained release tablets 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.

The following adverse effects occur with **TEVA-MORPHINE SR** 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

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: hyperalgesia

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

Post-Marketing Experience

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.

DRUG INTERACTIONS

Overview

Interactions with Central Nervous System (CNS) Depressants (including benzodiazepines and alcohol): **TEVA-MORPHINE SR** (morphine sulfate sustained release tablets) should be dosed with caution and started in a reduced dosage in patients who are currently talking other central nervous system depressants (e.g., other opioids, anaesthetics, sedatives, hypnotics, antidepressants, phenothiazines, neuroleptics, antihistamines and antiemetics) glutethimide or gabapentin, and beta-blockers, as they may enhance the CNS-depressant effect (e.g., respiratory depression) of **TEVA-MORPHINE SR**. **TEVA-MORPHINE SR** should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

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 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 **CONTRAINDICATIONS).**

Serotonergic Agents: Coadministration of morphine sulfate with a serotonergic agent, such as a selective serotonin re-uptake inhibitor or a serotonin norepinephrine re-uptake inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS, Neurologic**).

Drug-Food Interactions

Food has no significant effect on the extent of absorption of morphine from morphine sulfate sustained release tablet.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interaction
The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

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 of TEVA-MORPHINE SR (morphine sulfate sustained release tablets) 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 DOSAGE AND ADMINISTRATION - Adjustment or Reduction of Dosage).

Dosing Considerations
TEVA-MORPHINE SR (morphine sulfate sustained release tablets) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.

TEVA-MORPHINE SR 15 mg, 30 mg, 60 mg 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 WARNINGS AND PRECAUTIONS).

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 **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

TEVA-MORPHINE SR tablets are not indicated for rectal administration.

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

Recommended Dose and Dosage Adjustment

Adults: 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 the younger age group.

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, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy.

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.

Patients Not Receiving Opioids at the Time of Initiation of Morphine 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** 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.

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.

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]

Opiods	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

Dose Titration: Dose titration is the key to success with morphine 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 **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 **WARNINGS AND PRECAUTIONS**). Tapering should be individualized and carried out under medical supervision.

Patient 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, postherpetic 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.

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.

Disposal

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.

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.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: Serious overdosage with morphine may be characterized by respiratory depression (respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), dizziness, confusion, extreme somnolence progressing to stupor or coma, pneumonia aspiration, miosis, rhabdomyolysis progressing to renal failure, hypotonia, cold and clammy skin, 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.

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacodynamics

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

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

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

Morphine produces respiratory depression by direct action on brain stem respiratory centres. It depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

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

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

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 morphine sulfate sustained release tablet must be individualized (see **DOSAGE AND ADMINISTRATION**) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

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.

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.

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

Geriatrics: 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.

STORAGE AND STABILITY

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.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

TEVA-MORPHINE SR (morphine sulfate sustained release tablets) are available as:

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.

Composition

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 #10/Aluminum Lake
FD&C Blue #1/Aluminum Lake
FD&C Red #40/ Aluminum Lake

30 mg: FD&C Blue #2/ Aluminum Lake
D&C Red #27/Aluminum Lake
FD&C Yellow #6/Aluminum Lake

60 mg: FD&C Yellow #6/Aluminum Lake

FD&C Red #40/Aluminum Lake

100 mg: FD&C Blue #2/Aluminum Lake
FD&C Yellow #6/Aluminum Lake
FD&C Red #40/Aluminum Lake

200 mg: D&C Red #30/Aluminum Lake
FD&C Red #40/Aluminum Lake

Packaging

TEVA-MORPHINE SR 15 mg tablets are supplied in bottles of 50.
TEVA-MORPHINE SR 30 mg, 60 mg, 100 mg and 200 mg tablets are supplied in bottles of 50 and 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

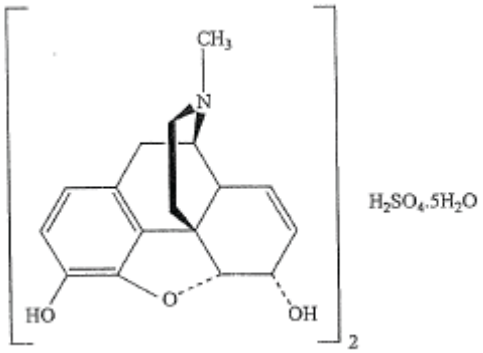
Proper name: morphine sulfate

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:



Description: Morphine sulfate is a white or almost white crystalline powder. Morphine sulfate is soluble 1:21 in water and 1:1000 in ethanol. It is practically insoluble in ether or chloroform.

CLINICAL STUDIES

SUMMARY TABLES:

A randomized, two period, two treatment crossover comparative bioavailability study of Teva-Morphine SR (sustained-release) 15 mg tablets (Teva Canada Limited, Canada) and MS Contin® 15 mg sustained-release tablets (Purdue Pharma, Canada) administered as a single 1 x 15 mg dose, was conducted in 34 healthy adult male and female subjects under fed conditions. A summary of the bioavailability data is presented below.

Morphine (1x 15 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng_*h/mL)	53.284 55.066 (27)	52.958 54.638 (25)	100.62	96.81 - 104.57
$AUC_{(0-12)}$ (ng_*h/mL)	40.504 41.696 (25)	39.793 40.966 (24)	101.79	97.95 - 105.78
AUC_I (ng_*h/mL)	60.319 61.347 (26)	58.688 60.122 (22)	102.78	99.37 - 106.31
C_{max} (ng/mL)	8.109 8.401 (25)	8.784 9.222 (33)	92.32	85.04 - 100.21
T_{max}§ (h)	2.79 (48)	2.72 (46)		
$T_{½}$§ (h)	12.17 (35)	13.05 (32)		

* Teva-Morphine SR Tablets 15 mg (Teva Canada Limited, Canada)

† MS Contin® 15 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.

§ Expressed as the arithmetic mean (CV %) only

A randomized, two period, two treatment crossover comparative bioavailability study of Teva-Morphine SR (sustained-release) 15 mg tablets (Teva Canada Limited, Canada) and MS Contin® 15 mg sustained-release tablets (Purdue Pharma, Canada) administered as a single 1 x 15 mg dose, was conducted in 22 healthy adult male and female subjects under fasting conditions. A summary of the bioavailability data is presented below.

Morphine (1 x 15 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (ng*h/mL)	52.667 54.631 (27)	53.373 55.504 (27)	98.68	95.05 – 102.44
AUC_{0-12} (ng*h/mL)	36.189 37.405 (25)	37.755 39.086 (26)	95.85	92.76 – 99.05
AUC_{inf} (ng*h/mL)	58.850 62.263 (22)	59.879 61.014 (25)	98.28	94.51 – 102.21
C_{max} (ng/mL)	6.298 6.519 (27)	6.800 7.048 (26)	92.61	87.62 – 97.90
T_{max} § (h)	1.75 (55)	1.74 (72)		
$T_{½}$ § (h)	10.78 (68)	11.19 (42)		

* Teva-Morphine SR Tablets 15 mg (Teva Canada Limited, Canada)

† MS Contin® 15 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.

§ Expressed as the arithmetic mean (CV %) only

A randomized, two period, two treatment crossover comparative bioavailability study of Teva-Morphine SR (sustained-release) 15 mg tablets (Teva Canada Limited, Canada) and MS Contin® 15 mg sustained-release tablets (Purdue Pharma, Canada) administered as a a multiple-dose 1 x 15 mg (q12h), was conducted in 20 healthy adult male and female subjects under fasting conditions. A summary of the bioavailability data is presented below.

Morphine (1 x 15 mg, q12h) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_{tau} (ng_*h/mL)	61.637 63.162 (23)	62.059 63.687 (24)	99.32	94.61 - 104.26
C_{max} (ng/mL)	8.634 8.804 (20)	9.347 9.601 (24)	92.37	87.57 – 97.42
C_{min} (ng/mL)	2.481 2.604 (35)	2.322 2.490 (38)	106.85	93.01 – 122.74
T_{max}§ (h)	2.30 (57)	1.98 (58)		
FL§ (%)	119.88 (19)	135.45 (22)		

***** Teva-Morphine SR Tablets 15 mg (Teva Canada Limited, Canada)

† MS Contin® 15 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.

§ Expressed as the arithmetic mean (CV %) only

A randomized, two period, two treatment crossover comparative bioavailability study of Teva-Morphine SR (sustained-release) 200 mg tablets (Teva Canada Limited, Canada) and MS Contin® 200 mg sustained-release tablets (Purdue Pharma, Canada) administered as a single 1 x 200 mg dose, was conducted in 28 healthy adult male and female subjects under fed conditions. A summary of the bioavailability data is presented below.

Morphine (1x 200 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng_*h/mL)	957.661 1023.926 (44)	962.002 1017.232 (43)	99.55	96.51 - 102.68
$AUC_{(0-12)}$ (ng_*h/mL)	647.855 677.971 (33)	632.479 656.155 (32)	102.43	98.66 - 106.35
AUC_I (ng_*h/mL)	1012.937 1082.006 (45)	1024.003 1083.680 (45)	98.92	95.79 - 102.15
C_{max} (ng/mL)	106.752 113.304 (37)	108.112 115.107 (38)	98.74	89.53 - 108.90
T_{max} § (h)	4.07 (37)	3.82 (65)		
$T_{½}$ § (h)	10.15 (28)	11.46 (28)		

* Teva-Morphine SR Tablets 200 mg (Teva Canada Limited, Canada)

† MS Contin® 200 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.

§ Expressed as the arithmetic mean (CV %) only

A randomized, two period, two treatment crossover comparative bioavailability study of Teva-Morphine SR (sustained-release) 200 mg tablets (Teva Canada Limited, Canada) and MS Contin® 200 mg sustained-release tablets (Purdue Pharma, Canada) administered as a single 1 x 200 mg dose, was conducted in 19 healthy adult male and female subjects under fasting conditions. A summary of the bioavailability data is presented below.

Morphine (1 x 200 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng_*h/mL)	878.020 901.993 (23)	813.662 843.039 (25)	107.91	99.88 – 116.59
AUC_I (ng_*h/mL)	910.635 936.033 (23)	845.628 878.553 (26)	107.69	99.17 – 116.94
C_{max} (ng/mL)	84.958 90.453 (34)	69.899 75.132 (36)	121.54	112.58 – 131.22
T_{max}§ (h)	2.91 (33)	2.64 (44)		
$T_{½}$§ (h)	9.70 (22)	9.97 (24)		

* Teva-Morphine SR Tablets 200 mg (Teva Canada Limited, Canada)

† MS Contin® 200 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.

§ Expressed as the arithmetic mean (CV %) only

A randomized, two period, two treatment crossover comparative bioavailability study of Teva-Morphine SR (sustained-release) 200 mg tablets (Teva Canada Limited, Canada) and MS Contin® 200 mg sustained-release tablets (Purdue Pharma, Canada) administered as a multiple-dose 1 x 200 mg (q12h), was conducted in 23 healthy adult male and female subjects under fasting conditions. A summary of the bioavailability data is presented below.

Morphine (1 x 200 mg, q12h) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_{tau} (ng_*h/mL)	1232.468 1290.281 (30)	1086.101 1148.681 (34)	113.48	105.59 - 121.96
C_{max} (ng/mL)	160.345 169.748 (34)	137.237 144.065 (34)	116.84	110.05 - 124.05
C_{min} (ng/mL)	57.085 60.330 (33)	47.985 54.161 (45)	118.97	105.34 - 134.36
T_{max}§ (h)	3.70 (24)	3.39 (44)		
FL§(%)	101.02 (25)	98.63 (37)		

* Teva-Morphine SR Tablets 200 mg (Teva Canada Limited, Canada)

† MS Contin® 200 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.

§ Expressed as the arithmetic mean (CV %) only

DETAILED PHARMACOLOGY

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 sulfated 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 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.

TOXICOLOGY

Animal

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

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

Human

Morphine toxicity may result from overdosage but because of the great interindividual 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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[N]TEVA-MORPHINE SR
Morphine Sulfate Sustained Release Tablets
15 mg, 30 mg, 60 mg, 100 mg and 200 mg

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 that can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).**

- **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 for the long-term management of pain, when:
- the pain is severe enough to require daily, around-the-clock pain medication
- the doctor determines that other treatment options are not able to effectively manage your pain

TEVA-MORPHINE SR 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 an oral sustained release tablet that slowly releases morphine over a 12 hour period. **TEVA-MORPHINE SR** contains morphine which is a pain medication belonging to the class of

medicines known as opioids which includes codeine, fentanyl and oxycodone. 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: **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 #10/Aluminum Lake FD&C Blue #1/Aluminum Lake FD&C Red #40/ Aluminum Lake
30 mg:	FD&C Blue #2/ Aluminum Lake D&C Red #27/Aluminum Lake FD&C Yellow #6/Aluminum Lake
60 mg:	FD&C Yellow #6/Aluminum Lake FD&C Red #40/Aluminum Lake
100 mg:	FD&C Blue #2/Aluminum Lake FD&C Yellow #6/Aluminum Lake FD&C Red #40/Aluminum Lake
200 mg:	D&C Red #30/Aluminum Lake FD&C Red #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.

Do not use TEVA-MORPHINE SR if:

- your doctor did not prescribe it for you
- you are allergic to morphine, other opioids, 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 pain medications, including those available without a prescription
- you have severe asthma, trouble breathing, or lung problems

you have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen

- you have a head injury
- if you are at risk for seizures
- you suffer from alcoholism
- you are taking, or have taken within the past 2 weeks, a monoamine oxidase inhibitor medication (e.g. phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are pregnant or plan to become pregnant, breast-feeding, or in labour

- are going to have, or recently had a planned surgery

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 severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have problems with your thyroid, adrenal or prostate gland
- have past or current depression
- suffer from chronic or severe constipation
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines

Other warnings you should know about:

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

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.

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
- lightheadedness

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

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 doctor may do tests, give you another medication, and slowly take you off **TEVA-MORPHINE SR**.

Serotonin syndrome: TEVA-MORPHINE SR can cause serotonin syndrome, a rare but potentially lifethreatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin syndrome if you take **TEVA-MORPHINE SR** with certain antidepressants or migraine medications.

Serotonin syndrome 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.

Sexual Function/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.

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

The following may interact with TEVA-MORPHINE SR:

- alcohol, including prescription and non-prescription medications containing alcohol.
- Do not drink alcohol while taking **TEVA-MORPHINE SR**. This can lead to drowsiness, depressed breathing, unusually slow or weak breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by **TEVA-MORPHINE SR**
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take **TEVA-MORPHINE SR** with monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with **TEVA-MORPHINE SR**
- drugs used to treat serious mental or emotional disorders, such as schizophrenia antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medication (beta blockers)
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- St. John's Wort

How to take TEVA-MORPHINE SR:
TEVA-MORPHINE SR tablets are designed to work properly over 12 hours when swallowed whole.

TEVA-MORPHINE SR 100 mg and 200 mg tablets are for use in "opioid tolerant" patients only. Your doctor will tell you when you are "opioid tolerant" to a certain dose of TEVA-MORPHINE SR.

Swallow whole. Do not cut, break, chew, dissolve or crush since this can cause the release of the entire 12-hour dose of morphine, which can seriously harm you. Only the 200 mg tablet is scored and may be broken in half. The half tablet must also be swallowed intact.

TEVA-MORPHINE SR tablets must be taken regularly, every 12 hours (with or without food and with sufficient fluid, e.g., 4 to 6 oz. of water), to treat pain.

Usual Adult Starting Dose:
Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor. Taking higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor 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.

Should your pain increase or any other complaint as a result of taking **TEVA-MORPHINE SR**, tell your doctor immediately.

Stopping your Medication:
You should not stop taking **TEVA-MORPHINE SR** all at once if you have been taking it for more than a few days.
Your doctor 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 with 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 doctor each time you need more **TEVA-MORPHINE SR**. Therefore, it is important that you contact your doctor before your current supply runs out.

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

Overdose:

If you think you have taken too much **TEVA-MORPHINE SR**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- abnormally slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:

It is important that you do not miss any doses. If you miss a dose, take your next dose at your usual time. You should always try to get back on track with your regular dosing schedule (e.g., 8 o'clock in the morning and 8 o'clock in the evening). If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using TEVA-MORPHINE SR?

These are not all the possible side effects you may feel when taking **TEVA-MORPHINE SR**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Constipation
- Dizziness
- Drowsiness
- Dry mouth
- Headache
- Itching
- Lack of muscle strength
- Nausea and/or vomiting
- Sweating
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using **TEVA-MORPHINE SR**.

If nausea and vomiting become troublesome during prolonged therapy with **TEVA-MORPHINE SR**, talk to your doctor or pharmacist

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	
Rare	**Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin.			√
	Respiratory Depression: Slow, shallow or weak breathing.			√
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
	Withdrawal: nausea, vomiting, diarrhea, anxiety,		√	

	shivering, cold and clammy skin, body aches, loss of appetite, sweating.			
	Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
	Low Blood Pressure: dizziness, fainting, light-headedness.	√		
	Serotonin Syndrome: agitation or restlessness, less of muscle control or muscle twitching, tremor, diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Keep unused or expired TEVA-MORPHINE SR in a secure place to prevent theft, misuse or accidental exposure.

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 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.

Disposal:

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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.
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This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

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