

Drug Interactions (See also: **WARNINGS**)

Use with CNS Depressants

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol may produce additive depressant effects. Respiratory depression, hypotension, and profound sedation or coma may occur. When such combined therapy is contemplated, the use of one or both agents should be reduced. Opioid analgesics, including Morphine Sulfate Controlled-Release Tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential on the effect on fertility have not been conducted.

Pregnancy

Pregnancy Effects - CATEGORY C

Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the fetus.

Morphine Sulfate Controlled-Release Tablets should be used in pregnant women only if the need for strong opioid analgesia clearly outweighs the potential risk to the fetus. (See also: **PRECAUTIONS: Labor and Delivery, and WARNINGS: DRUG ABUSE AND ADDICTION.**)

Labor and Delivery

Morphine Sulfate Controlled-Release Tablets is not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

Neonatal Withdrawal Syndrome

Chronic maternal use of opioids during pregnancy can affect the fetus with subsequent withdrawal symptoms. Neonatal withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, abnormal crying, tremor, vomiting, diarrhea and subsequent weight loss or failure to gain weight, and may result in death. The onset, duration and severity of neonatal withdrawal syndrome varies based on the drug used, duration of use, the dose of last maternal use, and rate of elimination by the newborn. Use standard care as medically appropriate.

Nursing Mothers

Low levels of morphine have been detected in the breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving Morphine Sulfate Controlled-Release Tablets since morphine may be excreted in the milk.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Morphine Sulfate Controlled-Release Tablets are not to be chewed, crushed, dissolved or divided for administration.

Geriatric Use

Clinical studies of Morphine Sulfate Controlled-Release Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression, res-

piratory arrest, shock, and cardiac arrest.

Most Frequently Observed

Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoria.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed Reactions

Central Nervous System: Weakness, headache, agitation, tremor, uncoordinated muscle movements, seizure, alterations of mood (nervousness, apprehension, depression, floating feelings), dreams, muscle rigidity, transient hallucinations and disorientation, visual disturbances, insomnia, increased intracranial pressure.

Gastrointestinal: Dry mouth, biliary tract spasm, laryngospasm, anorexia, diarrhea, cramps, taste alteration, constipation, ileus, intestinal obstruction, dyspepsia, increases in hepatic enzymes

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension, hypertension

Genitourinary: Urine retention or hesitance, amenorrhea, reduced libido and/or potency

Dermatologic: Pruritus, urticaria, other skin rashes, edema, diaphoresis

Other: Anticholinergic effect, parosmia, bronchospasm, muscle tremor, blurred vision, nystagmus, diplopia, miosis, anisotropia

OVERDOSAGE

Acute overdosage with morphine can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, rhinorrhea progressing to renal failure, and, sometimes, bradycardia, hypotension, and death. The nature of the controlled-release morphine should also be taken into account when treating the overdose. Even in the case of improvement, continued medical monitoring is required because of the possibility of extended effects. Deaths due to overdose may occur with abuse and misuse of Morphine Sulfate Controlled-Release Tablets.

In the treatment of morphine overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid agonists, such as naloxone, are specific antidotes against respiratory depression which results from opioid overdose. Naloxone should be administered intravenously; however, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered, as needed, or given by continuous infusion to maintain alertness and respiratory function; however, there is no information available about the cumulative dose of naloxone that may be safely administered.

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

Note: In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with care and by titration with smaller than usual doses of the antagonist.

DOSAJE AND ADMINISTRATION
(SEE ALSO CLINICAL PHARMACOLOGY, WARNINGS, AND PRECAUTIONS SECTIONS)

MORPHINE SULFATE CONTROLLED-RELEASE TABLETS IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO OTHER OPIOID AGONISTS. MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA CAN BE ABUSED AND ARE SUBJECT TO CRIMINAL DIVERSION.

Morphine Sulfate Controlled-Release TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, DISSOLVED OR

CRUSHED, TAKING BROKEN, CHEWED, DISSOLVED, OR CRUSHED MORPHINE SULFATE CONTROLLED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF POTENTIALLY FATAL DOSE OF MORPHINE.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as those outlined by the World Health Organization, the Federation of State Medical Boards Model Guideline for American Pain Society. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see BOXED WARNING).

Morphine Sulfate Controlled-Release Tablets is a controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM.) However, Morphine Sulfate Controlled-Release Tablets do not release morphine continuously over the course of a dosing interval. The administration of single doses of Morphine Sulfate Controlled-Release Tablets on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater variability in morphine plasma level has not been systematically evaluated.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of initial dose and dosing interval of Morphine Sulfate Controlled-Release Tablets, attention should be given to 1) the daily dose, potency, and precise characteristics of the opioid to be used; 2) the patient's history (e.g., whether it is a pure agonist or mixed agonist/antagonist); 2) the reliability of the relative potency estimate used to calculate the dose of morphine needed (N.B., potency estimates may vary substantially); 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a complex clinical decision in the management of the pain of an individual patient.

During periods of changing analgesic requirements including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient, and the caregiver/family.

Conversion from Immediate-Release Oral Morphine to Morphine Sulfate Controlled-Release Tablets

A patient's daily morphine requirement is established using immediate-release oral morphine (dosing every 4 to 6 hours). The patient is then converted to Morphine Sulfate Controlled-Release Tablets in either of two ways: 1) by administering one-half of the patient's 24-hour requirement as Morphine Sulfate Controlled-Release Tablets on an every 12-hour schedule, or 2) by administering one-third of the patient's daily requirement as Morphine Sulfate Controlled-Release Tablets on an every eight hour schedule. With either method, the morphine requirement is then adjusted as needed (see discussion below). The 15 mg tablet should be used for initial conversion for patients whose total daily requirement is expected to be less than 60 mg. The 30 mg tablet strength is recommended for patients with a daily morphine requirement of 60 to 120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Controlled-Release Tablets

Morphine Sulfate Controlled-Release Tablets can be administered as the initial oral morphine drug product; in this case, however, particular care must be exercised in the conversion process. Because of uncertainty about, and intersubject variability in, relative estimates of opioid potency and cross tolerance, initial dosing regimens should be conservative. It is better to underestimate the 24-hour oral morphine requirement than to overestimate. To this end, initial, individual doses of Morphine Sulfate Controlled-Release Tablets should be estimated conservatively. In patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day, the 30 mg tablet strength is recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted

to the 60 mg or 100 mg tablet strength, or an appropriate combination of tablet strengths, if desired.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and possibly, by an individual's medical condition. Consequently, it is difficult to recommend any fixed rule for converting a patient to Morphine Sulfate Controlled-Release Tablets directly. The following general points should be considered, however:

1. *Parenteral to oral morphine ratio:* Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only three times the daily parenteral morphine requirement may be sufficient in chronic use settings.
2. *Other parenteral or oral opioids to oral morphine:* Because there is lack of systematic evidence bearing on these types of analgesic substitutions, specific recommendations are not possible.

Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safer to underestimate the daily dose of Morphine Sulfate Controlled-Release Tablets required and rely upon ad hoc supplementation to deal with inadequate analgesia. (See discussion which follows.)

Use of Morphine Sulfate Controlled-Release Tablets as the First Opioid Analgesic

There has been no systematic evaluation of Morphine Sulfate Controlled-Release Tablets as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using a controlled-release morphine, it is ordinarily advisable to begin treatment using an immediate-release formulation. (See Special Instructions for Morphine Sulfate Controlled-Release 100 and 200 mg Tablets)

Considerations in the Adjustment of Dosing Regimens

Whatever the approach, if a dose of excessive opioid effects occurs early in a dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, "breakthrough" pain occurs late in the dosing interval, the dosing interval may be shortened. Alternatively, a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief, opioid side effects, and the convenience of the dosing schedule.

In adjusting dosing requirements, it is recommended that the dosing interval need not be extended beyond 12 hours because the administration of very large single doses may lead to acute overdose. (N.B. Morphine Sulfate Controlled-Release Tablets is a controlled-release formulation; it does not release morphine continuously over the dosing interval.)

For patients with low daily morphine requirements, the 15 mg tablet should be used.

Special Instructions for Morphine Sulfate Controlled-Release 100 and 200 mg Tablets
(For use in opioid-tolerant patients only)

Morphine Sulfate Controlled-Release 100 mg and 200 mg Tablets are for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 200 mg or more for the 100 mg tablet and 400 mg or more for the 200 mg tablet. It is recommended that these strengths be reserved for patients that have already been titrated to a stable analgesic regimen using lower strengths of Morphine Sulfate Controlled-Release Tablets or other opioids.

Supplemental Analgesia

When patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (including incident pain).

Continuation of Therapy

The intent of the titration period is to establish a patient-specific daily dose that will provide adequate analgesia with acceptable side effects and minimal rescue doses (2 or less) for as long as pain relief is necessary. Should pain recur, the dose can be increased to re-establish pain control as outlined above. During chronic, around-the-clock opioid therapy, the need for around-the-clock therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with Morphine Sulfate Controlled-Release Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Morphine Sulfate Controlled-Release Tablets to Parenteral Opioids

When converting a patient from Morphine Sulfate Controlled-Release Tablets to parenteral opioids, it is best to assume that the parenteral potency is higher. NOTE THAT THIS IS THE CONVERSE OF THE STRATEGY USED WHEN THE DIRECTION OF CONVERSION IS FROM THE PARENTERAL TO ORAL FORMULATIONS. IN BOTH CASES, HOWEVER, THE AIM IS TO ESTIMATE THE NEW DOSE CONSERVATIVELY. For example, to estimate the required 24-hour dose of morphine for IM use, one could employ a conversion of 1 mg of morphine IM for every 6 mg of morphine as Morphine Sulfate Controlled-Release Tablets. The IM 24-hour dose would have to be divided by six and administered on a q4h regimen. This approach is recommended because it is least likely to cause overdose.

SAFETY AND HANDLING

Morphine Sulfate Controlled-Release Tablets contain morphine sulfate which is a controlled substance under Schedule II of the Controlled Substances Act. Morphine, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to flush any unneeded Morphine Sulfate Controlled-Release Tablets down the toilet.

Morphine Sulfate Controlled-Release Tablets may be targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

MORPHINE SULFATE CONTROLLED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, DISSOLVED, OR CRUSHED. TAKING BROKEN, CHEWED, DISSOLVED, OR CRUSHED MORPHINE SULFATE CONTROLLED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

Morphine Sulfate Controlled-Release 100 mg and 200 mg Tablets are for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 200 mg or more for the 100 mg tablet and 400 mg or more for the 200 mg tablet. This strength is potentially fatal if accidentally ingested and patients and their families should be instructed to take special care to avoid accidental or intentional ingestion by individuals other than those for whom the medication was originally prescribed.

HOW SUPPLIED

Morphine Sulfate Controlled-Release Tablets 15 mg are round, lavender-colored, film-coated tablets bearing the symbol ABG on one side and 15 on the other. They are supplied as follows:

NDC 0591-3511-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Controlled-Release Tablets 30 mg are round, lavender-colored, film-coated tablets bearing the symbol ABG on one side and 30 on the other. They are supplied as follows:

NDC 0591-3512-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Controlled-Release Tablets 60 mg are round, orange-colored, film-coated tablets bearing the symbol ABG on one side and 60 on the other. They are supplied as follows:

NDC 0591-3513-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Controlled-Release Tablets 100 mg are round, gray-colored, film-coated tablets bearing the symbol ABG on one side and 100 on the other. They are supplied as follows:

NDC 0591-3514-01: opaque plastic bottles containing 100 tablets

Morphine Sulfate Controlled-Release Tablets 200 mg are capsule-shaped, green-colored, film-coated tablets bearing the symbol ABG on one side and 200 on the other. They are supplied as follows:

NDC 0591-3515-01: opaque plastic bottles containing 100 tablets

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container.

CAUTION

DEA Order Form Required.

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