MORPHINE SULFATE RECTAL SUPPOSITORIES

(WARNING: MAY BE HABIT FORMING)

DESCRIPTION
Each suppository for rectal administration contains 5 mg, 10 mg, 20 mg, or 30 mg of Morphine Sulfate in a blend, specifically formulated Hydrogentrated Vegetable Oil Base with BSA and BHT as preservatives, as well as other ingredients.

Chemically, Morphine Sulfate is, Morphinan-3, 6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-(Sx,Bx)-sulfate (2:1) (salt), pentahydrate, which can be represented by the following structural formula:

\[
\text{HO O OH} \quad \text{CH}_2 \quad \text{H} \quad \text{N} \quad \text{CH}_3 \quad 2 \quad \text{CH}_2
\]

CLINICAL PHARMACOLOGY
Morphine is a potent narcotic analgesic; it is its principal therapeutic effect is relief of pain. In addition to analgesia, narcotics produce drowsiness, changes in mood, and mental clouding; although neither sensory modalities nor motor activity are blocked at therapeutic doses. There is no intrinsic limit to the analgesic effect. Clinically, however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, nausea, and vomiting, which can result from high doses.

Morphine has diverse additional actions. It depresses the respiratory center, stimulates the cough reflex, decreases the depth of respiration, constricts the pupils, increases the tone of gastrointestinal and genitourinary tracts, and produces miosis. Morphine is detoxified in the liver by means of conjugation with glucuronic acid. Small amounts of the free drug and larger amounts of conjugated morphine are present in the urine, and these account for most of the administered drug. Ninety percent of the total excretion occurs within the first 24 hours.

Morphine is about two-thirds absorbed from the gastrointestinal tract with the maximum analgesic effect occurring 20-60 minutes post administration.

INDICATIONS AND USAGE
Morphine is indicated for the relief of severe chronic pain, and severe acute pain.

CONTRAINDICATIONS
Hypersensitivity to morphine; respiratory insufficiency or depression; severe CNS depression; attack of bronchial asthma; heart failure secondary to chronic lung disease; cardiac arrhythmias; increased intracranial or cerebrospinal pressure; head injuries; brain tumor; acute alcohol, delirium tremens; convulsions; after biliary tract surgery; suspected surgical anastomosis; concomitantly with MAO inhibitors or within 14 days of such treatment.

WARNINGS
Morphine can cause tolerance, psychological and physical dependence. Withdrawal will occur on abrupt discontinuation or administration of a narcotic antagonist. Interaction with Other Central-Nervous-System Depressants - Morphine should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

PRECAUTIONS
General
Head Injury and Increased Intracranial Pressure - The respiratory depressant effects of morphine and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, morphine must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions - Morphine should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with substantially decreased respiratory reserve, existing or impending respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect - The administration of morphine may result in severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Supraventricular Tachycardias - Caution should be used in patients with atrial flutter and other supraventricular tachycardias due to a possible vagolytic action which may produce a significant increase in the ventricular response rate.

Special Risk Patients - Morphine should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison’s disease, prostatic hypertrophy, or uremia.

Convulsions - Morphine may aggravate preexisting convulsive disorders. Convulsions may occur in individuals without a history of convulsive disorders if dosage is escalated above recommended levels because of tolerance development.

Acute Abdominal Conditions - The administration of morphine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Use in Ambulatory Patients - Morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Morphine, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Patients should be cautioned about the combined effects of alcohol or other central nervous system depressants with morphine.

Drug Interactions - Generally, effects of morphine may be potentiated by alkylating agents and antagonized by acidifying agents. Analgesic effects of morphine may be potentiated by chlorpromazine and meperidine. CNS-depressants such as anesthetics, hypnotics, barbiturates, phenothiazines, chloral hydrate, glutethimide, sedatives, MAO inhibitors (including procarbazine hydrochloride), antihistamines, beta-blockers (propranolol), alcohol, furazolidone and other narcotics may enhance the depressive effects of morphine.

Morphine may increase anticoagulant activity of the

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PREGNANCY
Teratogenic Effects - Pregnancy Category C: Animal reproduction studies have not been con-
ducted. It is also not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Morphine should be given to a pregnant woman only if clearly needed.

Labor and Delivery - Morphi ne readily crosses the placental barrier and if administered during labor may lead to respiratory depression in the neonate.

Nursing Mothers - Morphine has been detected in human milk. If morphine is administered to a nursing mother, caution should be exercised when morphine is administered to a nursing woman. Pediat ric Usage - Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The major hazards of morphine, as with other narcotic analgesics, are respiratory depression and, to a lesser extent, circulatory arrest. Shock and car-
di ac arrest have occurred.

The most frequently observed adverse re-
cations include lightheadedness, dizziness, seda-
tion, nausea, vomiting and sweating. These effects seem to be more prominent in ambu-
latory patients and in those who are not suffering severe pain. In such individuals, smaller doses are advisable. Some adverse reactions may be alleviated in the ambulatory patient who lies down.

Other adverse reactions include the following:

Central Nervous System - Drowsiness, depression, headache, incoordination, dis-
orientation, and visual disturbances.

Gastrointestinal - Dry mouth, anorexia, consti-
tion, and biliary tract spasm.

Cardiovascular - Flushing of the face, bradycar-
dia, palpitation, faintness and syncope.

Genitourinary - Urinary retention or hesitancy, anti-
diuretic effect, and reduced libido and/or potency.

Allergic - Pruritus, urticaria, other skin rashes, edema, and rarely hemorrhagic urticaria.

Treatment of the most frequent adverse reac-
tions:

Constipation - Ample intake of water or other liquids, stool softeners, and adequate physical activity may prevent this. Senna may be administered if constipation does not occur for two days, an enema should be administered to prevent impaction.

In the event diarrhea occurs, seepage around a fecal impaction is a possible cause to consider before diarrheal measures are employed.

Nausea and Vomiting - Phenoxybenzine and antihista
mines can be effective treatments for nau-
sea of the medullary and vestibular sources respectively. However, these drugs may poten-
tiate the side effects of the narcotic or the antina-
useant.

Drowsiness (sedation) - Once pain control is achieved, undesirable sedation can be mini-
imized by titrating the dose. A slight drowsiness that just maintains a tolerable pain or pain free state is acceptable.

DRUG ABUSE AND DEPENDENCE
Morphine Sulfate is a Schedule II controlled substance. As with other narcotic analgesics patients may develop a physical and psycholog-
ical dependence on morphine. They may increase dosage without consulting a physician and the ultimate extent of such dependence may be determined by the maintenance dosage of the drug. In such cases, abrupt discontinuance may precipitate typical with-
drawal symptoms, including convulsions. Therefore, the drug should be withdrawn grad-
ually from any patient known to be taking excessive doses over a long period of time.

In treating the terminally ill patient the benefit of pain relief may outweigh the possibility of drug dependence. The chance of drug dependence is substantially reduced when the patient is placed on scheduled narcotic programs instead of a “pain in relief of pain” cycle typical of a PRN regimen.

OVERDOSE
Signs and Symptoms: Serious overdosage is characterized by respirato-
ry depression (a decrease in respiratory rate and depth), cyanosis, severe somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension.

Treatment of Overdose:

Primary attention should be given to the reestablish-
ment of adequate respiratory exchange through provision of a patent airway and institu-
tion of assisted or controlled ventilation. If depressed respiration is associated with muscular rigidity, an IV neuromuscular blocking agent may be required to facilitate assisted or controlled res-
piration.

The narcotic antagonists-nalorphine, naloxone, and levalorphan are specific antidotes against respiratory depression resulting from overdosage with respect to sensitivity to narcotics. Thus, an antagonist should be administered, preferably by the IV route, simultaneously with efforts at respi-
atory resuscitation. Since the duration of action of nalorphine and naloxone is shorter than that of the antagonist, repeated doses of the antagonist may be required to maintain adequate respiration; the patient must be kept under surveillance.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should also be employed as indicated. In cases of oral overdose, the stom-
ach should be evacuated by emesis or gastric lavage if treatment can be instituted within 2 hours of the last dose. The patient should be observed closely for a rise in temperature or pul-
monary complications that may signal the need for institutionalization.

DOSAGE AND ADMINISTRATION FOR MOR-
PHINE SULFATE SUPPOSITORIES
Usual Adult Dose: 10 to 20 mg every 4 hours or as directed by physician.

Dosage is a patient dependent variable, therefore incremental dosage increases may be required to achieve ade-
quately.

Note: Medication may suppress respiration in the elderly, the very ill, and those patients with respi-
ratory problems, therefore lower doses may be required.

Morphine Dosage Reduction: During the first two to three days of effective pain relief, the patient may be able to reduce the morphine dose pre-
pared as the effect of excessive analgesic dosing rather than the first sign of relief of a pain exhausted patient. Therefore, despite a dose reduction at three days before reduc-
ion, if respiratory adequacy or vital sign criteria are adequate.

The following successful relief of severe pain, period-
ic attempts to reduce the narcotic dose should be made. A slow and continuous reduction of the narcotic analgesic may become feasible due to a physiologic change or the improved mental state of the patient.

MORPHINE SULFATE SUPPOSITORY
Schedule II Narcotic DEA Order Form Required

A Schedule II Narcotic

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.