

PRODUCT MONOGRAPH

^NMS Contin[®]

**Morphine Sulfate Sustained Release Tablets
5, 15, 30, 60, 100 and 200 mg**

^NMS Contin[®] Suppositories

**Morphine Sulfate Sustained Release Suppositories
30, 60, 100, 200 and 300 mg**

**Purdue Pharma Std.
Opioid Analgesic**

Purdue Pharma
575 Granite Court
Pickering, ON
L1W 3W8

Control No. 130745

DATE OF REVISION:
August 25, 2009

PRODUCT MONOGRAPH

NAME OF DRUG

^NMS Contin[®]

Morphine Sulfate Sustained Release Tablets
5, 15, 30, 60, 100 and 200 mg

^NMS Contin[®] Suppositories

Morphine Sulfate Sustained Release Suppositories
30, 60, 100, 200 and 300 mg

PHARMACOLOGICAL CLASSIFICATION

Opioid Analgesic

ACTIONS

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 CO₂, 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.

Morphine is readily absorbed when given orally, rectally or by s.c. or i.m. injection. Due to "first-pass" metabolism in the liver, the effect of an oral dose is less than after parenteral administration. With repeated regular dosing, oral morphine is about 1/3 as potent as when given by intramuscular injection and rectal **MS Contin[®]** (morphine sulfate sustained release suppositories) has

approximately 40% the potency of subcutaneous morphine. The rectal dose of **MS Contin** suppositories is approximately equivalent to the oral dose of **MS Contin[®]** (morphine sulfate sustained release tablets) after repeated dosing. 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.

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. **MS Contin** suppositories given 12 hourly provide equivalent pain control to **MS Contin** tablets given orally at the same dose and frequency, or to morphine administered subcutaneously at a dose approximately 40% of the daily rectal dose.

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.

Comparison of **MS Contin** suppositories and tablets indicates attainment of peak concentrations at 4.1 and 4.3 hours post-dose respectively. The extent of absorption of **MS Contin** suppositories at steady state is equivalent to that of **MS Contin** tablets and approximately 40% of that of subcutaneous morphine.

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 **MS Contin** tablets and 60 - 1200 mg/day in the case of **MS Contin** suppositories.

INDICATIONS

MS Contin[®] (morphine sulfate sustained release) is indicated for the relief of severe pain requiring the prolonged use of an opioid analgesic preparation.

CONTRAINDICATIONS

MS Contin[®] (morphine sulfate sustained release) should not be given to patients with: hypersensitivity to opioid analgesics, morphine or any other component of the product; acute asthma or other obstructive airway disease and acute respiratory depression; cor pulmonale; cardiac arrhythmias; acute alcoholism; delirium tremens; severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; brain tumor; suspected surgical abdomen (e.g., paralytic ileus); concomitant MAO inhibitors (or within 14 days of such therapy).

WARNINGS

MS Contin[®] (morphine sulfate sustained release tablets) 5, 15, 30, 60 and 100 mg tablets must be swallowed whole, and must not be chewed, dissolved or crushed. Taking 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 should also be swallowed intact.

MS Contin 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 MS Contin 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 **MS Contin**, as it may increase the chance of experiencing dangerous side effects (see **PRECAUTIONS**, Drug Interactions).

MS Contin is not recommended for preoperative use or postoperatively within the first 24 hours.

Abuse of Opioid Formulations: **MS Contin** consists of a polymer matrix intended for oral use only.

Abuse can lead to overdose and death. This risk is increased when the tablets are crushed, broken, dissolved or chewed, and with concurrent consumption of alcohol or other CNS depressants. 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.

Drug Dependence: As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of morphine and there is potential for abuse of the drug and for development

of strong psychological dependence. **MS Contin** should therefore be prescribed and handled with the high degree of caution appropriate to the use of a drug with strong abuse potential. Drug abuse is not usually a problem in patients with severe pain in which morphine is appropriately indicated. However, in the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for drug abuse. Withdrawal symptoms may occur following abrupt discontinuation of morphine therapy or upon administration of an opioid antagonist. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

Use in Drug and Alcohol Addiction: **MS Contin** 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.

CNS Depression: 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 and other CNS depressants (including alcohol). Respiratory depression, hypotension and profound sedation or coma may result.

Severe pain antagonizes the subjective and respiratory depressant actions of morphine. Should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive **MS Contin** within 24 hours of the procedure.

Use in Pregnancy: Animal studies with morphine and other opioids have indicated the possibility of teratogenic effect. In humans, it is not known whether morphine can cause fetal harm when administered during pregnancy or can affect reproductive capacity. **MS Contin** should be given to pregnant patients only if clearly needed and when the anticipated benefits outweigh the potential risks to the fetus.

PRECAUTIONS

Respiratory Depression: Morphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. Such patients are often less sensitive to the stimulatory effects of carbon dioxide on the respiratory center and the respiratory depressant effects of morphine may reduce respiratory drive to the point of apnea.

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.

Hypotension: Morphine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of such drugs as phenothiazines or certain anaesthetics.

Acute Abdominal Conditions: 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.

Special Risk Groups: Morphine should be administered with caution and in a reduced dosage to elderly or debilitated patients, to patients with severely reduced hepatic or renal function, and to patients with adrenocortical insufficiency (e.g., Addison's disease), biliary tract disorders, hypothyroidism, pancreatitis, prostatic hypertrophy or urethral stricture.

Morphine should not be used where there is the possibility of paralytic ileus occurring.

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

Use during Labour/Delivery and in Nursing Mothers: Morphine crosses the placental barrier and its administration during labour can produce respiratory depression in the neonate. Morphine has been detected in human breast milk. Caution should be exercised if morphine is administered to a nursing mother.

Driving and Operating Dangerous Machinery: Morphine 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.

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. CNS depressants such as other opioids, anaesthetics, sedatives, hypnotics, neuroleptics, other tranquilizers, chloral hydrate, glutethimide or gabapentin, may enhance the depressant effect of morphine and may result with respiratory depression, hypotension, profound sedation or coma. Monoamine oxidase inhibitors (including procarbazine hydrochloride) should not be taken within two weeks of use. Pyrazolidone antihistamines, beta-blockers and alcohol may also enhance the depressant effect of morphine. When combined therapy is contemplated, the dose of one or both agents should be reduced.

“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 **MS Contin** tablets. The clinical significance of these findings is unknown.

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.

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

ADVERSE REACTIONS

The major hazards associated with morphine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following oral or parenteral use of morphine.

Most Common Adverse Effects Requiring Medical Attention:

The most frequently observed side effects of opioid analgesics such as morphine are sedation, nausea, vomiting, constipation, lightheadedness, dizziness and hyperhidrosis.

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 and vomiting occur frequently after single doses of opioids or as an early unwanted effect of regular opioid therapy. When instituting prolonged therapy for chronic pain, the routine prescription of an antiemetic should be considered. Patients taking the equivalent of 20 mg or more of oral morphine every four hours (60 mg q12h of **MS Contin[®]** [morphine sulfate sustained release]) usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so but may persist due to opioid-induced gastric stasis. In such patients, metoclopramide is often useful.

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.

Other Adverse Reactions Include:

Cardiovascular: faintness, hypotension, palpitations, syncope and supraventricular tachycardia

CNS: agitation, confusion, convulsions, dizziness, dysphoria, euphoria, hallucinations, headache, insomnia, involuntary muscle contractions, malaise, mood altered, paresthesia, somnolence, thinking disturbances, vertigo, visual disturbances and weakness

Dermatologic: edema, other skin rashes, pruritus, and urticaria

Endocrine: 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)

Gastrointestinal: abdominal pain, anorexia, biliary tract spasm, constipation, cramps, dry mouth, dyspepsia, gastrointestinal disorders, ileus, increased hepatic enzymes, nausea, taste perversion and vomiting

General: allergic reaction, anaphylactic reaction, ^hanaphylactoid reaction, asthenia, drug dependence, drug tolerance, drug withdrawal syndrome, facial flushing, hyperhidrosis, hypertonia and miosis

Genitourinary: amenorrhea, decreased libido or potency, erectile dysfunction, urinary retention or hesitance

Metabolic and Nutritional: peripheral edema

Respiratory: bronchospasm, cough decreased, pulmonary edema and respiratory depression

Withdrawal (Abstinence) Syndrome: 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. The following withdrawal symptoms may be observed after opioids are discontinued: body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, stomach cramps, tachycardia, tremors or shivering, trouble with sleeping, unexplained fever, hyperhidrosis, weakness and yawning. With appropriate medical use of opioids and gradual withdrawal from the drug, these symptoms are usually mild.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Symptoms: Serious morphine overdose is characterized by respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), extreme somnolence progressing to stupor or coma, rhabdomyolysis progressing to renal failure, flaccidity of skeletal muscle, cold or clammy skin, and sometimes hypotension and bradycardia. 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 overdose 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 overdose 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 i.v. 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.

DOSAGE AND ADMINISTRATION

MS Contin 5, 15, 30, 60 and 100 mg tablets must be swallowed intact, not chewed, dissolved or crushed. Taking 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 should also be swallowed intact.

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 strong 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.

For essential information on the important details of the management of cancer pain, the reader may wish to consult the following resources:

Cancer pain: a monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Twycross RG, Lack SA. Symptom control in far advanced cancer: pain relief. London: Pitman, 1983.

Adult Dose: 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.

The suppository may be used in situations where the patient cannot tolerate oral dosing. Up to two suppositories of the same or varying strengths may be used at one time, to achieve the required dose

for 12 hourly administration. In some patients using **MS Contin** suppositories, a reduction in frequency of administration of the same 12-hourly dose to once every 24 hours, followed by dose titration, as appropriate, may provide an adequate duration of pain control.

Suppository administration is achieved by finger length insertion into the rectum, with the patient in a reclining position. Where appropriate, patients should be encouraged to attempt a bowel movement prior to insertion of the suppository. When a bowel movement occurs after insertion of a suppository, loss of a portion of the dose is possible. In such cases, the dose of **MS Contin** suppositories should not be repeated until the next scheduled administration. In the intervening period, breakthrough pain should be managed with appropriate rescue analgesics.

Patients over the age of 50 tend to require much lower doses of morphine than in the younger age group. In elderly and debilitated patients and those with impaired respiratory function or significantly decreased renal function, the initial dose should be one half of the usual recommended dose.

Pediatric Dose: 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 **MS Contin** orally every 12 hours.

Patients Currently Receiving Opioids: Patients currently receiving other oral morphine formulations may be transferred to **MS Contin** at the same total daily morphine dosage, equally divided into two 12 hourly **MS Contin** 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, the following equivalence table 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 **MS Contin** doses. Some patients may require a lower dose on initial conversion, followed by further titration during chronic dosing, to maintain optimal analgesia.

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 (MS Contin) 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 **MS Contin**, 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 **MS Contin** tablets are 15, 30, 45, 60, 90, 120, 150, 180 and 200 mg. The usual recommended dose (q12h) increments for **MS Contin** suppositories are 30, 60, 90, 120, 160 and 200 mg. Above the 200 mg/dose (400 mg/day) increments should be by 30-60 mg/dose.

The 5 mg **MS Contin** tablet is intended only to supplement other available strengths in order to formulate an appropriate dose. Therefore, multiple 5 mg strength tablets should not be used as a substitute for higher strengths.

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

Adjustment or Reduction of Dosage: 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. If treatment discontinuation is required, the dose of opioid may be decreased as follows: one-half of the previous daily dose given q12h for the first two days, followed thereafter by a 25% reduction every two days.

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.

TABLE 1
OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES¹

Drug	Equivalent Dose (mg) ² (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10 ³	60 ³	3-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine ⁴	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone ⁵	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Oxycodone	-	10-15 ⁶	2-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists⁷:			
Pentazocine ⁴	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

References:

¹ Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.

Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

² Most of this data was derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.

³ For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2 - 3: 1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).

⁴ These drugs are not recommended for the management of chronic pain.

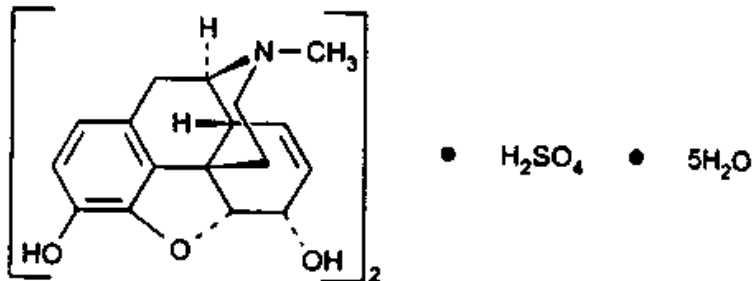
⁵ Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

⁶ In combination with acetaminophen or ASA. For acute pain, single entity oral oxycodone is twice as potent as oral morphine.

⁷ Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

PHARMACEUTICAL INFORMATION

The chemical name of morphine sulfate is 7,8,-didehydro-4,5 α -epoxy-17-methyl-morphinan-3, 6 α -diol sulfate (2:1) (salt) pentahydrate, and it has the following structure:



Molecular Formula: (C₁₇H₁₉NO₃) - H₂SO₄

Molecular Weight: 758.8 (pentahydrate)
668.8 (anhydrous)

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

Composition:

Active Ingredient(s): Morphine Sulfate

Non-Medicinal Ingredients - Tablets (*all strengths*): cetostearyl alcohol, hydroxyethyl cellulose, lactose (5, 15, 30, 60 mg only), magnesium stearate and talc

5 mg Film Coating: Opadry Y-1-7000 White

- hydroxypropyl methylcellulose
- titanium dioxide
- polyethylene glycol

15 mg Film Coating: Opadry[®] OY-8855 Green

- D&C Yellow No. 10 Aluminum Lake
- FD&C Blue No. 1 Aluminum Lake
- FD&C Blue No. 2 Aluminum Lake
- hydroxypropyl methylcellulose
- polyethylene glycol 400
- titanium dioxide

30 mg Film Coating: Opadry[®] YS-1-4729 Purple

- D&C Red No. 7 Calcium Lake
- FD&C Blue No. 2 Aluminum Lake
- FD&C Yellow No. 6 Aluminum Lake
- hydroxypropyl methylcellulose
- polyethylene glycol 400
- polysorbate 80
- titanium dioxide

60 mg Film Coating: Opadry[®] OY-3508 Orange
- D&C Yellow No. 10 Aluminum Lake
- FD & C Red No. 3 Aluminum Lake
- FD&C Yellow No. 6 Aluminum Lake
- hydroxypropyl methylcellulose
- polyethylene glycol 400
- titanium dioxide

100 mg Film Coating: Opadry[®] OY-8215 Grey
- FD&C Blue No. 2 Aluminum Lake
- hydroxypropyl methylcellulose
- iron oxide, yellow
- iron oxide, black
- polyethylene glycol 400
- titanium dioxide

200 mg Film Coating: Opadry[®] OY-5970
- FD&C Blue No. 2
- FD&C Red No. 3
- FD&C Yellow No. 6 Aluminum Lake
- hydroxypropyl methylcellulose
- polyethylene glycol 400
- titanium dioxide

Non-medicinal Ingredients - Suppositories (*all strengths*):

Calcium phosphate, glycerol tricocoate (*novata-b), sodium alginate.

(*Novata is a blend of tri, di, and monoglycerides of saturated fatty acids)

Stability and Storage Recommendations:

Store tablets and suppositories at room temperature (15° - 30° C).

The suppositories may also be refrigerated.

AVAILABILITY

MS Contin[®] (morphine sulfate sustained release tablets) are available in 5 mg (white), 15 mg (green), 30 mg (violet), 60 mg (orange), 100 mg (grey) and 200 mg (red) strengths. The tablets are film-coated, bi-convex and imprinted with PF on one side and 5 mg, 15 mg, 30 mg, 60 mg, 100 mg or 200 mg (as appropriate) on the reverse. The 5, 15, 30, 60 and 100 mg tablets are round and the 200 mg strength is capsule-shaped. The 200 mg tablet (only) is scored and may be broken in half.

MS Contin 15, 30, 60, 100 and 200 mg tablets are supplied in opaque, plastic bottles containing 50 tablets and in blister packs of 25 tablets. **MS Contin** 5 mg tablets are supplied in opaque, plastic bottles containing 50 tablets.

MS Contin suppositories are available in 30, 60, 100, 200 and 300 mg strengths and are supplied in strips of six, with four strips to a carton.

INFORMATION FOR THE CONSUMER

Read this information carefully before you take MS Contin tablets or insert MS Contin suppositories. Also read the information you get with your prescription refills, since there may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if **MS Contin** is right for you. Share the information in this leaflet with members of your household.

What is morphine?

Morphine is a medicine used to treat severe pain and should help you live more comfortably and independently. Morphine belongs to a class of drugs which is commonly referred to as opiates, opioids or narcotics, and also includes codeine, fentanyl, hydromorphone and oxycodone.

Your pain may increase or decrease from time to time and your doctor may need to change the amount of morphine you take daily (daily dosage).

What is MS Contin?

MS Contin is a controlled release tablet containing the medicine morphine. **MS Contin** is made to slowly release morphine over a 12 hour period, and requires a dose every 12 hours to control your pain. **MS Contin** is used to treat severe pain requiring the prolonged use of an opioid analgesic preparation.

MS Contin tablets are available in six strengths: 5 mg (white), 15 mg (green), 30 mg (violet), 60 mg (orange), 100 mg (grey), and 200 mg (red). **MS Contin** suppositories are available in five strengths:

30 mg, 60 mg, 100 mg, 200 mg and 300 mg strengths. It may be necessary for you to take more than one tablet strength (different coloured tablets) or use more than one suppository strength at the same time, in order to receive the total daily dosage prescribed by your doctor. You should not take **MS Contin** 100 or 200 mg tablets unless you are already taking the 60 mg strength, or an equivalent dose of a similar pain medication, and your doctor has instructed you to switch to the higher strength tablets.

Before you take MS Contin:

Your doctor should know about all of your medical conditions before deciding if **MS Contin** is right for you and what daily dosage is best. Tell your doctor about all of your medical problems, especially the following ones: trouble breathing or lung problems; head injury; liver or kidney problems; gastrointestinal problems; low blood pressure; prostate problems; urethral stricture (unusual narrowing of the urethra); adrenal gland problems, such as Addison's disease; convulsions or seizures; alcoholism; hallucinations or other severe mental problems; past or present substance abuse or drug addiction.

You should also tell your doctor if you are pregnant, breast-feeding, or intend to become pregnant while receiving **MS Contin** as this drug may not be right for you in these circumstances.

MS Contin should not be used if:

- your doctor did not prescribe it for you;
- your pain is mild;

- your pain can be controlled by occasional use of other painkillers;
- you have experienced severe allergic reactions (e.g., severe rash, hives, breathing problems, swelling of the mouth, tongue, face, or other areas or dizziness) while taking any opioid, including morphine, or any of the non-medicinal ingredients, in the past;
- you have severe asthma or severe lung problems;
- you have an irregular heartbeat;
- you suffer from alcoholism;
- you have a head injury;
- you have a brain tumour;
- you suffer from seizures;
- you had surgery less than 24 hours ago.

How to take MS Contin:

MS Contin 5, 15, 30, 60 and 100 mg tablets must be swallowed whole and should not be broken, chewed, crushed or dissolved, since this can cause the release of too much morphine, which can seriously harm you. Only the 200 mg tablet is scored and may be broken in half. The half tablet should also be swallowed intact.

You should not consume alcohol while taking MS Contin, as it may increase the chance of experiencing dangerous side effects.

MS Contin Tablets:

Follow your doctor's directions exactly. **MS Contin** tablets must be taken regularly every 12 hours (with 4 to 6 oz. of water) to prevent pain all day and night. If your pain worsens, making you uncomfortable, contact your doctor immediately and she/he may decide that it is necessary to adjust your daily dosage of **MS Contin**.

MS Contin Suppositories:

MS Contin suppository administration is achieved by finger length insertion into the rectum (after removing the plastic and foil packaging), while lying on your back. If you have the urge for a bowel movement, it is better to insert the suppository after the bowel movement. If you have a bowel movement after insertion of the suppository, do not insert another **MS Contin** suppository until the next scheduled dose.

MS Contin suppositories must be inserted regularly every 12 hours, or as directed by your doctor, to prevent pain all day or night. If your pain worsens, making you uncomfortable, contact your doctor immediately to ascertain if it is necessary to adjust your daily dosage of **MS Contin** suppositories. Your daily dosage of **MS Contin** will be clearly labelled on the medication bottle. Be sure to follow these directions exactly; this is very important. Do not increase or decrease your daily dosage without consulting your doctor. If your daily dosage is changed by your doctor, be sure to write it down at the time your doctor calls you or sees you and follow the new directions exactly. Regularly discuss your pain control and any side effects with your doctor to determine if you still need **MS Contin**. Be sure to use **MS Contin** only for the condition for which it was prescribed.

Stopping MS Contin:

Consult your doctor for instructions on how to discontinue taking **MS Contin**. You should not stop taking **MS Contin** all at once if you have been taking it for more than a few days, since this may lead to uncomfortable symptoms.

After you stop taking **MS Contin**, you should take the unused tablets or suppositories to your pharmacist to be destroyed.

Side effects you may have while taking MS Contin:

The most common side effects you may experience are constipation, nausea, drowsiness, dizziness, vomiting, itching, headache, dry mouth, weakness and sweating. Tell your doctor about these problems if they arise. Your doctor may prescribe a laxative and/or stool softener to help relieve constipation while you are taking **MS Contin**.

If you experience any symptoms related to difficulty in breathing, such as tight chest or wheezing, fainting, or rapid heartbeat, tell your doctor or pharmacist immediately.

Overdose:

The most important signs of overdose are suppressed breathing (abnormally slow or weak breathing), dizziness, confusion or extreme drowsiness. In case of suspected overdose, or if any of these symptoms occur, call your doctor and/or your local emergency number and/or a Regional Poison Control Centre immediately, even though you do not feel sick.

Taking MS Contin with other medications:

You should not take **MS Contin** if you are currently taking (or recently stopped taking) one of the medicines known as monoamine oxidase inhibitors (e.g. Nardil[®], Parnate[®]).

Tell your doctor about all medicines that you are taking. Your doctor should decide whether you can take **MS Contin** with other medicines. These include:

- other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, amphetamines, chlorpromazine, methocarbamol, tranquilizers, some heart medications (e.g., beta-blockers), blood-thinners (coumarin or other anticoagulants), chloral hydrate and glutethimide (not available in Canada) and gabapentin;
- antihistamines or sleep aids (these medicines could depress your breathing or your level of consciousness);
- medicines that you buy yourself without a prescription;
- any herbal remedies that you may be taking.

Driving/Other Activities:

Driving, operating hazardous machinery, or other tasks requiring full alertness should not be attempted for the first few days of taking **MS Contin**, or after your daily dosage is changed, since you may experience drowsiness or sedation. If drowsiness or sedation occurs, do not undertake such activities until you have talked with your doctor.

Abuse, Addiction and Physical Dependence:

There is a risk of abuse or addiction with all opioids. Some patients, particularly those who may have abused drugs in the past, may have a higher risk of abusing or developing an addiction while using opioids, such as **MS Contin**.

Patients who have taken **MS Contin** for a period of time may develop physical dependence, and should not abruptly stop taking it. However, physical dependence is not the same as addiction.

If you have concerns about abuse, addiction or physical dependence, please tell your doctor.

Reordering MS Contin:

A new written prescription is required from your doctor each time you need more **MS Contin**. Therefore, it is important that you contact your doctor at least three working days before your current supply runs out.

It is very important that you do not miss any doses. If you miss one dose, take it as soon as possible, but if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once, unless your doctor tells you to. If you miss several doses in succession, talk to your doctor before restarting.

Do not seek additional prescriptions for **MS Contin** from any other doctor - unless responsibility for your pain management has been transferred to another doctor.

Should your pain increase or any other complaint develop as a result of taking **MS Contin**, tell your doctor immediately.

Storage of MS Contin:

MS Contin contains an opioid medicine and must be stored in a secure place to prevent theft and misuse. Do not give **MS Contin** to anyone other than the person for whom it was prescribed since it may seriously harm them, including death. Keep **MS Contin** out of the reach of children. Accidental overdose by a child is dangerous and may result in death. Keep **MS Contin** in a cool, dry place, between 15 and 30°C. The suppositories may be refrigerated.

This leaflet summarizes important information about **MS Contin**. If you would like more information, talk with your doctor and/or pharmacist or contact the manufacturer, Purdue Pharma, at 1-800-387-5349.

PHARMACOLOGY

Morphine is a phenanthrene alkaloid obtained from opium. Morphine and related compounds interact with specific receptors primarily found in the brain, spinal cord and the myenteric plexus of the gut wall.

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.

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.

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.

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.

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.

The ratio of the rectal dose of **MS Contin** suppositories to the oral dose of **MS Contin** tablets is 1:1 based on pharmacokinetic data. Rectally administered morphine has, in some studies, shown a somewhat greater extent of absorption than oral morphine, which may be due to partial avoidance of hepatic first pass elimination by this route.

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. The mean elimination half-life of morphine is 2 to 3 hours with great interpatient variability. The major route of elimination is via the kidney. About 7 to 10% is excreted in the feces via the bile. 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-etheral sulfate. Route-specific differences in metabolite concentration were demonstrated in a pharmacokinetic study between oral and rectal administration of morphine. The mean AUC molar ratios of M6G and M3G to morphine were greater after oral morphine administration compared with rectal morphine administration. Systemic bioavailability and peak plasma concentration of M6G and M3G were significantly greater after oral morphine administration compared with the rectal route. Conversely, the systemic bioavailability of morphine was lower after oral administration although it was not statistically significant. Therefore rectal administration of morphine may be associated with significant avoidance of hepatic biotransformation.

Oral absorption of **MS Contin** tablets is equivalent to that of immediate-release tablets or liquid formulations and is not significantly affected by administration in the presence of food.

In a steady-state crossover study utilizing **MS Contin** 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 **MS Contin** 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.

In a single dose bioavailability study in healthy human volunteers, the area under the plasma concentration time curve was approximately 40% greater following **MS Contin** suppositories than **MS Contin** tablets. Maximum plasma morphine concentration with the suppository was approximately 70% of that achieved with the tablets. The steady-state bioavailability of **MS Contin** suppositories was demonstrated in two crossover studies in cancer patients, one utilizing **MS Contin** tablets as the reference formulation and the other subcutaneously administered morphine. When given at the same dose and frequency, **MS Contin** tablets and suppositories provided an equivalent extent of morphine absorption and peak concentrations were achieved, at 4.1 hours post-dose, compared with 4.3 hours for oral administration. Subcutaneous administration, at a daily dose approximately 2.5 times less than the dose of **MS Contin** suppositories resulted in a similar mean area under the plasma concentration time curve, indicating a bioavailability of 42% for the rectal route relative to the subcutaneous route. The relationship between mean plasma concentration and dose of **MS Contin** suppositories was found to be linear over a dose range of 60 - 1200 mg/day, and the mean time of maximum plasma morphine concentration was 3.2 hours post-dose.

TOXICOLOGY

Animal:

<u>Acute:</u>	<u>Oral LD₅₀</u>
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.

REFERENCES

1. Babul N, Darke AC. Disposition of morphine and its glucuronide metabolites after oral and rectal administration: evidence of route specificity. *Clin Pharmacol Ther* 1993;54:286-92.
2. Babul N, Darke AC, Anslow JA, Krishnamurthy TN. Pharmacokinetics of two novel rectal controlled release morphine formulations. *J Pain Symptom Manage* 1992;7:400-5.
3. Bianchi G, Ferretti P, Recchia M, Rocchetti M, Tavani A, Manara L. Morphine tissue levels and reduction of gastrointestinal transit in rats. Correlation supports primary action site in the gut. *Gastroenterology* 1983;85:852-8.
4. Bruera E, Belzile M, Neumann CM, Ford I, Harsanyi Z, Darke AC. Twice-daily versus once-daily morphine sulfate controlled-release suppositories for the treatment of cancer pain. *Support Care Cancer* 1999;7:280-3.
5. Brunk SF, Delle M. Morphine metabolism in man. *Clin Pharmacol Ther* 1974;16:51-7.
6. Bullingham RE, Moore RA, Symonds HW, Allen MC, Baldwin D, McQuay HJ. A novel form of dependency of hepatic extraction ratio of opioids in vivo upon the portal vein concentration of drug: comparison of morphine, diamorphine, fentanyl, methadone and buprenorphine in the chronically cannulated cow. *Life Sci* 1984;34:2047-56.
7. Cronin CM, Kaiko RF, Healy N, Grandy RP, Thomas G, Goldenheim PD. Controlled-release oral morphine insensitivity to a high fat meal. *J Clin Pharmacol* 1988;28:944.
8. Dickson PH, Lind A, Studts P, Nipper HC, Makoid M, Makoid M, et al. The routine analysis of breast milk for drugs of abuse in a clinical toxicology laboratory. *J Forensic Sci* 1994;39(1):207-14.

9. Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.
10. Ferrell B, Wisdom C, Wenzl C, Brown J. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol Nurs Forum* 1989;16(4):521-6.
11. Goughnour BR, Arkininstall WW, Stewart JH. Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients: *Cancer* 1989;63:2294-7.
12. Goughnour BR, Arkininstall WW. Potential cost-avoidance with oral extended-release morphine sulfate tablets versus morphine sulfate solution. *Am J Hosp Pharm* 1991;48:101-4.
13. Hanks GW, Trueman T. Controlled-release morphine tablets are effective in twice-daily dosage in chronic cancer pain. In: Wilkes E, Levy J, editors. *Advances in morphine therapy/the 1983 International Symposium on Pain Control*. New York: Oxford University Press;1984. p.103-5.
14. Henriksen H, Knudsen J. MST Continus tablets in pain of advanced cancer: a controlled study. In: Wilkes E, Levy J, editors. *Advances in morphine therapy/the 1983 International Symposium on Pain Control*. New York: Oxford University Press;1984. p.123-6.
15. Drug therapy of severe, chronic pain in terminal illness. *Ann Intern Med* 1983;99:870-3.
16. Jaffee JH, Mertin WR. Opioid analgesics and antagonists. In: Goodman LS, Gilman A, Gilman AG, editors. *The Pharmacological Basis of Therapeutics*. 6th ed. New York: Macmillan Press; 1980. p. 494-534.

17. Kaiko RF, Grandy RP, Oshlack B, Pav J, Horodniak J, Thomas G, et al.. The United States experience with oral controlled-release morphine (MS Contin[®] tablets). Parts I and II. Review of nine dose titration studies and clinical pharmacology of 15-mg, 30-mg, 60-mg and 100-mg tablet strengths in normal subjects. *Cancer* 1989;63:2348-54.
18. Knodell RG, Farleigh RM, Steele NM, Bond JH. Effects of liver congestion on hepatic drug metabolism in the rat. *J Pharmacol Exp Ther* 1982;221:52-7.
19. Lamerton RC. Evaluation of MST Continus tablets 60 mg and 100 mg in the treatment of pain in terminal illness - a hospice overview. In: Wilkes E, Levy J, editors. *Advances in morphine therapy/the 1983 International Symposium on Pain Control*. New York: Oxford University Press;1984. p.85-9.
20. McQuay HJ, Moore RA, Bullingham RES, Carroll D, Baldwin D, Allen MS, et al. High systemic relative bioavailability of oral morphine in both solution and sustained-release formulation. In: Wilkes E, Levy J, editors. *Advances in morphine therapy/the 1983 International Symposium on Pain Control*. New York: Oxford University Press;1984. p.149-54.
21. Mignault GG, Latreille J, Viguié F, Richer P, Lemire F, Harsanyi Z, et al. Control of cancer-related pain with MS Contin: a comparison between 12-hourly and 8-hourly administration. *J Pain Symptom Manage* 1995;10(6):416-22.
22. Misra AL. Metabolism of opiates. [Factors affecting the action of narcotics.] In: Adler ML, Manara L, Samanin R, editors. *New York: Raven Press; 1978. p. 197-343.*
23. Moore A, Sear J, Baldwin D, Allen M, Hunnise A, Bullingham R, McQuay H. Morphine kinetics during and after renal transplantation. *Clin Pharmacol Ther* 1984;35:641-5.

24. Patwardhan RV, Johnson RF, Hoyumpa A Jr., Sheehan JJ, Desmond PV, Wilkinson GR, Branch RA, Schenker S. Normal metabolism of morphine in cirrhosis. *Gastroenterology* 1981;81:1006-11.
25. Portenoy RK, Maldonado M, Fitzmartin R, Kaiko RF, Kanner R. Oral controlled-release morphine sulfate. Analgesic efficacy and side effects of a 100-mg tablet in cancer pain patients: *Cancer* 1989;63:2284-8.
26. Portenoy RK. Chronic opioid therapy in non-malignant pain. *J Pain Symptom Manage* 1990;5:S46-S62.
27. Portenoy RK, Foley KM, Intrussisi CE. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. *Pain* 1990;43:273-86.
28. Principles of analgesic use in the treatment of acute pain and cancer pain. 3rd ed. Illinois: American Pain Society; 1992.
29. Regnard CB, Randell F. Controlled-release morphine in advanced cancer pain. In: Wilkes E, Levy J, editors. *Advances in morphine therapy/the 1983 International Symposium on Pain Control*. New York: Oxford University Press;1984. p.142-4.
30. Thirlwell MP, Sloan PA, Maroun JA, Boos GJ, Besner JG, Stewart JH, et al. Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients: *Cancer* 1989;63:2275-83.
31. Stewart JJ, Weisbrodt NW, Burks TF. Central and peripheral actions of morphine on intestinal transit. *J Pharmacol Exp Ther* 1978;205:547-55.

32. Stimmel B. Pain, analgesia and addiction: the pharmacologic treatment of pain. New York: Raven Press, 1983.
33. Twycross RG, Lack SA. Symptom control in far advanced cancer: pain relief. London: Pitman; 1983.
34. United States. Management of Cancer Pain Guideline Panel. Management of cancer pain. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1994. Publication No. AHCPR94-0592.
35. Vandenberghe HM, Soldin SJ, MacLeod SM. Pharmacokinetics of morphine: a review. *Ther Drug Monit* 1982;11:1-5.
36. Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone;1994.
37. Walsh TD. Opiates and respiratory function in advanced cancer. *Recent Results Cancer Res* 1984;89:115-7.
38. Walsh TD. A controlled study of MST Continus tablets for chronic pain in advanced cancer.
39. Welsh J, Stuart JF, Habeshaw T, Blackie R, Whitehill D, Setanoians A, et al. A comparative pharmacokinetic study of morphine sulphate solution and MST Continus 30 mg tablets in conditions expected to allow steady-state drug level formulation. In: Stuart JF, editor. *Methods of morphine estimation in biological fluids and the concept of free morphine*. New York: Academic Press; 1981. p. 9-13.