PRODUCT MONOGRAPH

[N]NTP-MORPHINE SR

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

Teva Standard

Opioid Analgesic

Teva Canada Ltd.
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PRODUCT MONOGRAPH

NAME OF DRUG

^{N}NTP-MORPHINE SR
Morphine Sulfate Sustained Release Tablets
15, 30, 60, 100 and 200 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 CO_2 nausea and vomiting via stimulation of the CTZ, changes in mood including euphoria and dysphoria, sedation, mental clouding, and alterations of the endocrine and autonomic nervous systems.

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. 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.

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.

The relationship between mean plasma concentration and dose has been shown to be linear over a dosage range of 60 - 600 mg/day in the case of the morphine sulfate tablets.

INDICATIONS

NTP-MORPHINE SR (morphine sulfate sustained release) is indicated for the relief of severe pain requiring the prolonged use of an opioid analgesic preparation.

CONTRAINDICATIONS

NTP-MORPHINE SR (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; concomitant MAO inhibitors (or within 14 days of such therapy).

WARNINGS

NTP-MORPHINE SR (morphine sulfate sustained release tablets) 15, 30, 60 and 100 mg tablets must be swallowed whole, and must not be chewed or crushed. Taking broken, chewed 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.

NTP-MORPHINE SR 100 mg and 200 mg tablets are for use in opioid tolerant patients only (see also DOSAGE AND ADMINISTRATION). These tablet strengths may cause fatal respiratory depression if administered to patients not previously exposed to daily morphine equivalent dosages of 200 mg or more. Care should be taken in the prescribing of these tablet strengths.

Patients should be instructed not to give NTP-MORPHINE SR to anyone other than for whom it was prescribed, as such, inappropriate use may have severe medical consequences, including death.

Patients should be cautioned not to consume alcohol while taking NTP-MORPHINE SR, as it may increase the chance of experiencing dangerous side effects (see **PRECAUTIONS**, Drug Interactions).

NTP-MORPHINE SR is not recommended for preoperative use or postoperatively within the first 24 hours.

Abuse of Opioid Formulations: NTP-MORPHINE SR 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, 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. NTP-MORPHINE SR 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.

CNS Depression: Morphine should be used only with caution and in 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 NTP-MORPHINE SR 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. NTP-MORPHINE SR 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 reduced dosages, 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, barbiturates, phenothiazines, other tranquilizers, chloral hydrate and glutethimide 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 morphine sulphate 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 sweating.

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 NTP-MORPHINE SR [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, palpitations, postural hypotension, supraventricular tachycardia and syncope
CNS:	agitation, confusion, dizziness, dysphoria, euphoria, hallucinations, headache, insomnia, involuntary muscle contractions, malaise, mood changes, paresthesia, seizures, somnolence, thought abnormalities, vertigo, vision abnormalities and weakness
Dermatologic:	edema, pruritus, other skin rashes 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, elevated hepatic enzymes, gastrointestinal disorders, paralytic ileus, nausea, taste alterations and vomiting
General:	allergic reaction, anaphylactic/anaphylactoid reactions, asthenia, chills, drug dependence, facial flushing, hypertonia, miosis, sweating and tolerance
Genitourinary:	amenorrhea, reduced libido or potency, urinary retention or hesitance
Metabolic and Nutritional:	peripheral edema and pulmonary edema
Respiratory:	bronchospasm and cough decreased

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, unusual increase in sweating 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

Symptoms: Serious morphine overdosage is characterized by respiratory depression (reduced respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), extreme somnolence progressing to stupor or coma, 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 myosis may be seen with hypoxia in the setting of morphine overdose. Severe overdosage may result in apnea, circulatory collapse, cardiac arrest and death.

Treatment: Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial 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

NTP-MORPHINE SR 15, 30, 60 and 100 mg tablets must be swallowed intact, not chewed, or crushed. Taking broken, chewed 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.

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 patients 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 **NTP-Morphine SR** orally every 12 hours.

Patients Currently Receiving Opioids: Patients currently receiving other oral morphine formulations may be transferred to NTP-MORPHINE SR at the same total daily morphine dosage, equally divided into two 12 hourly NTP-MORPHINE SR doses.

For patients who are receiving an alternate opioid, the "oral morphine sulfate equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, 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 NTP-MORPHINE SR 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 the regular administration of the lowest dose of morphine which will maintain the patient free of pain at all times.**

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 NTP-MORPHINE SR, dosage adjustments should generally be separated by 48 hours. If dose increments turn out to be required, they should be proportionately greater at the lower dose level (in terms of percentage of previous dose), than when adjusting a higher dose. The usual recommended dose (q12h) increments for NTP-MORPHINE SR tablets are 15, 30, 45, 60, 90, 120, 150, 180 and 200 mg. Above the 200 mg/dose (400 mg/day) increments should be by 30-60 mg/dose.

NTP-MORPHINE SR 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. However, where judged necessary for optimization of drug effects, NTP-MORPHINE SR 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 EQUIVALENCES[1]

Drug	Equivalent Dose (mg)[2] (compared to morphine 10 mg i.m.)		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-Antagonists[7]:			
Pentazocine[4]	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

[1] References:

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.

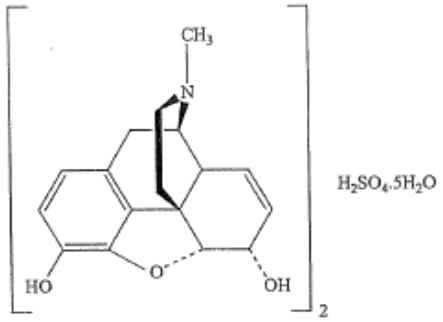
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Morphine Sulfate

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

Structural Formula:



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

Molecular Weight: 758.8 (pentahydrate)
668.76 (anhydrous)

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

Composition:
Active Ingredient(s): Morphine Sulfate

Non-medicinal Ingredients (all strengths): Colloidal Silicon Dioxide, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate and Stearic Acid

15 mg Film Coating: Opadry II Green 85F91277
Polyvinyl Alcohol - Partially Hydrolyzed
Polyethylene Glycol 3350
Talc
Titanium Dioxide
D&C Yellow #10/Aluminum Lake

	FD&C Blue #1/Brilliant Blue FCF Aluminum Lake FD&C Red #40/Allura Red AC Aluminum Lake
30 mg Film coating:	Opadry II Purple 85F10117 Polyvinyl Alcohol - Partially Hydrolyzed Polyethylene Glycol 3350 Talc Titanium Dioxide FD&C Blue #2/Indigo Carmine Aluminum Lake D&C Red #27/Phloxine Aluminum Lake FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake
60 mg Film Coating:	Opadry II Orange 85F13953 Polyvinyl Alcohol - Partially Hydrolyzed Polyethylene Glycol 3350 Talc Titanium Dioxide FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake FD&C Red #40/Allura Red AC Aluminum Lake
100 mg Film Coating:	Opadry II Gray 85F17684 Polyvinyl Alcohol - Partially Hydrolyzed Polyethylene Glycol 3350 Talc Titanium Dioxide FD&C Blue #2/Indigo Carmine Aluminum Lake FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake FD&C Red #40/Allura Red AC Aluminum Lake
200 mg Film Coating:	Opadry II Pink 85F14408 Polyvinyl Alcohol - Partially Hydrolyzed Polyethylene Glycol 3350 Talc Titanium Dioxide D&C Red #30/Helendo Pink Aluminum Lake FD&C Red #40/Allura Red AC Aluminum Lake

Stability and Storage Recommendations:
NTP-MORPHINE SR 15 mg tablets: store tablets at room temperature (15°C - 25°C). Protect from light.
NTP-MORPHINE SR 30, 60, 100 and 200 mg tablets: Store tablets at room temperature (15°C - 30°C). Protect from light.

AVAILABILITY

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

15 mg: Green, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 15 on the other side.
30 mg: Violet, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 30 on the other side.
60 mg: Orange, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 60 on the other side.
100 mg: Grey, round, sustained release, film-coated, biconvex tablets, engraved N on one side and 100 on the other side.
200 mg: Red, scored, caplet-shaped, sustained release, film-coated, biconvex tablets, engraved N scoreline N on one side and 200 on the other side.

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

INFORMATION FOR THE CONSUMER

Read this information carefully before you take NTP-MORPHINE SR tablets. 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 NTP-MORPHINE SR is right for you. Share the information in this leaflet with members of your household.

What is morphine?

Morphine is a medicine used to relieve 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 NTP-MORPHINE SR?

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

NTP-MORPHINE SR tablets are available in five strengths: 15 mg (green), 30 mg (violet), 60 mg (orange), 100 mg (grey), and 200 mg (red). You should not take NTP-MORPHINE SR 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 NTP-MORPHINE SR:

Your doctor should know about all of your medical conditions before deciding if NTP-MORPHINE SR 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 NTP-MORPHINE SR as this drug may not be right for you in these circumstances.

NTP-MORPHINE SR 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 NTP-MORPHINE SR:

NTP-MORPHINE SR 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 NTP-MORPHINE SR, as it may increase the chance of experiencing dangerous side effects.

Follow your doctor's directions exactly. NTP-MORPHINE SR 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 NTP-MORPHINE SR.

Your daily dosage of NTP-MORPHINE SR 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 NTP-MORPHINE SR. Be sure to use NTP-MORPHINE SR only for the condition for which it was prescribed.

Stopping NTP-MORPHINE SR:

Consult your doctor for instructions on how to discontinue taking NTP-MORPHINE SR. You should not stop taking NTP-MORPHINE SR 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 NTP-MORPHINE SR, you should take the unused tablets to your pharmacist to be destroyed.

Side effects you may have while taking NTP-MORPHINE SR:
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 NTP-MORPHINE SR.

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 immediately.

Taking NTP-MORPHINE SR with other medications:
You should not take NTP-MORPHINE SR 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 NTP-MORPHINE SR 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);
- 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 NTP-MORPHINE SR, 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 NTP-MORPHINE SR.

Patients who have taken NTP-MORPHINE SR 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 NTP-MORPHINE SR:
A new written prescription is required from your doctor each time you need more NTP-MORPHINE SR. 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 NTP-MORPHINE SR 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 NTP-MORPHINE SR, tell your doctor immediately.

Storage of NTP-MORPHINE SR:
NTP-MORPHINE SR contains an opioid medicine and must be stored in a secure place to prevent theft and misuse. Do not give NTP-MORPHINE SR to anyone other than the person for whom it was prescribed since it may seriously harm them. Keep NTP-MORPHINE SR out of the reach of children. Accidental overdose by a child is dangerous and may result in death. NTP-MORPHINE SR 15 mg tablets: store tablets at room temperature (15°C - 25°C). Protect from light. NTP-MORPHINE SR 30, 60, 100 and 200 mg tablets: Store tablets at room temperature (15°C - 30°C). Protect from light.

This leaflet summarizes important information about NTP-MORPHINE SR. If you would like more information, talk with your doctor and/or pharmacist or contact the manufacturer, Teva Canada Limited, at 1-800-268-4127 ext. 5005.

CLINICAL STUDIES

SUMMARY TABLES:

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

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

* NTP-Morphine SR Tablets 15 mg (Teva Canada Limited, Canada)
† MS Contin® 15 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.
§ Expressed as the arithmetic mean (CV %) only

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

Morphine (1 x 15 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (ng*h/mL)	52.667 54.631 (27)	53.373 55.504 (27)	98.68	95.05 – 102.44
AUC_{0-12} (ng_*h/mL)	36.189 37.405 (25)	37.755 39.086 (26)	95.85	92.76 – 99.05

Morphine (1 x 15 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{inf} (ng•h/mL)	58.850 62.263 (22)	59.879 61.014 (25)	98.28	94.51 – 102.21
C_{max} (ng/mL)	6.298 6.519 (27)	6.800 7.048 (26)	92.61	87.62 – 97.90
T_{max}§ (h)	1.75 (55)	1.74 (72)		
$T_{½}$§ (h)	10.78 (68)	11.19 (42)		

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

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

§ Expressed as the arithmetic mean (CV %) only

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

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

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

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

§ Expressed as the arithmetic mean (CV %) only

A randomized, two period, two treatment crossover comparative bioavailability study of NTP-Morphine SR (sustained-release) 200 mg tablets (Teva Canada Limited, Canada)

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

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

* NTP-Morphine SR Tablets 200 mg (Teva Canada Limited, Canada)
† MS Contin® 200 mg Sustained Release Tablets (Purdue Pharma, Canada). Purchased in Canada.
§ Expressed as the arithmetic mean (CV %) only

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

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

Morphine (1 x 200 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
T_{max}§ (h)	2.91 (33)	2.64 (44)		
$T_{½}$§ (h)	9.70 (22)	9.97 (24)		

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

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

§ Expressed as the arithmetic mean (CV %) only

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

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

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

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

§ Expressed as the arithmetic mean (CV %) only

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. In man, the principal pharmacological actions of morphine are in the CNS; analgesia, drowsiness, mood changes, mental clouding, respiratory depression, nausea or emesis, miosis and on smooth muscle; increased gastrointestinal tone with a reduction in propulsive motion, increased biliary pressure and increased tone of the ureter and vesical sphincter.

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.

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-ethereal 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 morphine sulphate 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 morphine sulphate tablets every 12 hours versus morphine sulfate solution every 4 hours in cancer patients, there was no significant difference between formulations in respect to the extent of absorption of morphine. The mean maximum concentration following morphine sulphate was approximately 15% higher than with morphine oral solution and was achieved at a mean of 3.4 hours post-dose compared with 1.2 hours for the solution. There was a linear relationship between mean plasma morphine concentration and dose over the range of 60 - 600 mg/day.

TOXICOLOGY

Animal:

Acute:	Oral LD50
Mice	650 mg/kg
Rats	460 mg/kg
Guinea Pigs	1000 mg/kg

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

Human: Morphine toxicity may result from overdosage but because of the great interindividual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal.

The presence of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggests that in a morphine naive, pain-free individual, the lethal oral dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity.

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39. A Single-Dose, Comparative Bioavailability Study of Two Formulations of Morphine Sulfate 15 mg Sustained Release Tablets Under Fasting Conditions. Data on file at Teva Canada Limited.

40. A Multiple-Dose, Comparative Bioavailability Study of Two Formulations of Morphine Sulfate Sustained Release Tablets 15 mg q12h Under Fasting Conditions. Data on file at Teva Canada Limited.

41. A Single-Dose, Comparative Bioavailability Study of Two Formulations of Morphine Sulfate 200 mg Sustained Release Tablets Under Fed Conditions. Data on file at Teva Canada Limited.

42. A Single-Dose, Comparative Bioavailability Study of Two Formulations of Morphine Sulfate 200 mg Sustained Release Tablets Under Fasting Conditions. Data on file at Teva Canada Limited.

43. A Multiple-Dose, Comparative Bioavailability Study of Two Formulations of Morphine Sulfate Sustained Release Tablets 200 mg q12h Under Fasting Conditions. Data on file at Teva Canada Limited.