# PRODUCT MONOGRAPH

## [N]Codeine Contin®

**Codeine Controlled Release Tablets**
**50, 100, 150 and 200 mg**
**Purdue Pharma Std.**

**Opioid Analgesic**

Purdue Pharma
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® Purdue Pharma, owner of the registered trademark Codeine Contin

# PRODUCT MONOGRAPH

## NAME OF DRUG

[N]Codeine Contin®
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## THERAPEUTIC CLASSIFICATION

Opioid Analgesic

## ACTIONS

Codeine is an opioid analgesic which exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, codeine 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, miosis and alterations of the endocrine and autonomic nervous systems.

Orally administered codeine is approximately 60% as potent as intramuscular codeine in terms of total analgesia. The relative potency of I.M. codeine phosphate is approximately 1/12 that of I.M. morphine sulfate and orally, 200 mg of codeine phosphate is equivalent to 20 - 30 mg of morphine sulfate during chronic dosing.

The analgesic efficacy of **Codeine Contin®** (codeine controlled release tablets) has been evaluated in multiple dose studies in patients with cancer pain and chronic non-malignant pain. In a dose-response study in cancer patients, **Codeine Contin** 150 mg every 12 hours provided approximately equivalent analgesia to 600 mg acetaminophen plus 60 mg codeine every 6 hours. In patients with cancer pain and chronic non-malignant pain receiving q4h p.r.n. acetaminophen plus codeine, **Codeine Contin** (100, 150 or 200 mg every 12 hours) produced improved pain control and reduced consumption of supplementary acetaminophen plus codeine. In patients with chronic low back pain, **Codeine Contin** (100 mg every 12 hours), supplemented with p.r.n. plain acetaminophen, produced lower pain scores and less fluctuation in pain throughout the day than p.r.n. acetaminophen plus codeine.

## Pharmacokinetics

Codeine is readily absorbed from the gastrointestinal tract and has an oral bioavailability of 53%, relative to the intramuscular route. Codeine is rapidly distributed from blood to body tissues, passes the blood-brain barrier and is found in fetal tissue and breast milk. Codeine is metabolized in the liver to morphine and norcodeine, each representing about 10% of the administered dose of codeine. Urinary excretion products are free and glucuronide-conjugated codeine (about 70%), free and conjugated morphine (about 10%), normorphine (under 4%) and hydrocodone (<1%). The remainder of the dose appears in the feces.

The conversion of codeine to morphine by CYP2D6 has a high degree of variability in humans. About 5-10 percent of Caucasians and 1 percent of Asians exhibit the poor metabolizer phenotype.

However a range of CYP2D6 activity levels, including very efficient metabolizers of codeine, have been documented (see **WARNINGS**, Ultra-Rapid Metabolizers of Codeine).

Given the higher potency of morphine relative to codeine, CYP2D6 activity levels have been associated with outcomes from codeine administration that range from an absence of effect to responses with the potential of serious medical consequences.

**Codeine Contin** is absorbed to an equivalent extent as immediate-release tablet or liquid formulations of codeine. In single dose studies in fasting, healthy volunteers, the maximum plasma codeine concentration ($C_{max}$) is approximately 56% of that from immediate-release formulations and is achieved approximately 2.6 times later - at 3.3 hours post-dosing. In steady-state studies in healthy volunteers, both the extent of absorption and maximum plasma codeine concentrations are equivalent to those from immediate-release formulations at the same total daily dose. In the presence of food, the extent of absorption of **Codeine Contin** is not significantly increased but peak concentrations are somewhat delayed, occurring at 3.9 - 4.5 hours post-dose.

## INDICATIONS

**Codeine Contin®** (codeine controlled release tablets) are indicated for the relief of mild to moderate pain requiring the prolonged use of an opioid analgesic preparation.

## CONTRAINDICATIONS

**Codeine Contin®** (codeine controlled release tablets) should not be given to patients with: a hypersensitivity to opioid analgesics; acute asthma or other obstructive airway disease and acute respiratory depression; cor pulmonale; acute alcoholism; delirium tremens; severe CNS depression; convulsive disorders; increased cerebrospinal or intracranial pressure; head injury; suspected surgical abdomen; concomitant MAO inhibitors (or within 14 days of such therapy), or who are pregnant, breast-feeding, in labour and during delivery.

## WARNINGS

**Codeine Contin® (codeine controlled release tablets) should be swallowed whole, and should 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 codeine. All strengths may be halved, except 50 mg. The half tablets should also be swallowed intact.**

**Patients should be instructed not to give Codeine 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 **Codeine Contin**, as it may increase the chance of experiencing dangerous side effects.

**Codeine Contin** should be used with caution preoperatively and within the first 24 hours postoperatively.

Ultra-Rapid Metabolizers of Codeine: Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labelled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

Abuse of Opioid Formulations: **Codeine 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 may develop upon repeated administration of codeine and there is potential for development of psychological dependence. **Codeine Contin** should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential. Drug abuse is not usually a problem in patients with pain in whom codeine is appropriately indicated. Withdrawal symptoms may occur following abrupt discontinuation of codeine 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: Codeine 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 opioid analgesics. 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 **Codeine Contin** within 24 hours of the procedure.

Use in Pregnancy: Animal studies with a number of opioids, including codeine, have indicated the possibility of teratogenic effects. In humans, it has not conclusively been established whether codeine can cause fetal harm when administered during pregnancy or can affect reproductive capacity.

Since codeine crosses the placental barrier, Codeine Contin is contraindicated in patients who are pregnant (see **CONTRAINDICATIONS**). Dependence and withdrawal signs have been reported in newborns whose mothers took opiates regularly during pregnancy. These signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting and diarrhea. Signs usually appear during the first few days of life.

**Lactation**: **Codeine Contin** is contraindicated in women who are breast-feeding (see **CONTRAINDICATIONS**). Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, **some women are ultra-rapid metabolizers of codeine (**see **WARNINGS,** Ultra-Rapid Metabolizers of Codeine**). These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.**

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Since there is a risk of infant exposure to codeine and morphine through breast milk **Codeine Contin** is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating paediatricians about any use of codeine during breast-feeding.

## PRECAUTIONS

Respiratory Depression: Codeine 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 codeine may reduce respiratory drive to the point of apnea.

Head Injury: The respiratory depressant effects of codeine, 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, codeine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, codeine must be used with extreme caution and only if it is judged essential.

Hypotension: Codeine 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: Codeine has been shown to decrease bowel motility. Codeine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Groups: Codeine should be administered with caution, and in reduced dosages, to elderly or debilitated patients, to patients with severely reduced hepatic or renal function, and in patients with Addison's disease, hypothyroidism, prostatic hypertrophy or urethral stricture.

Use during Labour/Delivery: **Codeine Contin®** (codeine controlled release tablets) is contraindicated in women who are in labour or delivery (see **CONTRAINDICATIONS**).

Codeine crosses the placental barrier and its administration during labor can produce respiratory depression in the neonate. If the mother has received narcotic analgesics during labour, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required.

Driving and Operating Dangerous Machinery: Codeine 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.

Drug Interactions: Patients should also be cautioned about the combined effects of codeine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol. The analgesic effect of codeine is potentiated by amphetamines, chlorpromazine and methocarbamol. CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, chloral hydrate and glutethimide may enhance the depressant effect of codeine. 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 codeine. 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 slight decrease in the rate of release of codeine from **Codeine Contin** tablets.

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 codeine. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of codeine and/or may precipitate withdrawal symptoms in these patients.

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

## ADVERSE REACTIONS

Adverse effects of **Codeine Contin®** (codeine controlled release tablets) are similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards associated with codeine, are respiratory and central nervous system depression and, to a lesser degree, circulatory depression.

The most frequently observed adverse effects are sedation, nausea, vomiting, constipation, light-headedness, dizziness, and sweating.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. 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, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia,

early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a chronic 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. Stimulant laxatives, stool softeners and other appropriate measures should be used as required.

Less Frequently Observed with Opioid Analgesics:

*General and CNS*: agitation, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), blurred vision, diplopia and miosis, dysphoria, euphoria, headache, insomnia, increased intracranial pressure, muscle rigidity, muscle tremor, nystagmus, paresthesia, transient hallucinations and disorientation, tremors, uncoordinated muscle movements, visual disturbances and weakness

*Cardiovascular*: bradycardia, chills, faintness, flushing of the face, hypertension, hypotension, palpitation, syncope and tachycardia

*Respiratory*: bronchospasm and laryngospasm

*Gastrointestinal*: anorexia, biliary tract spasm, cramps, diarrhea, dry mouth and taste alterations

*Genitourinary*: antidiuretic effects, urinary retention or hesitancy

*Dermatologic*: diaphoresis, other skin rashes, pruritus and urticaria

Withdrawal (Abstinence) Syndrome: Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids. 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, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, unexplained fever, weakness and yawning. In patients who are appropriately treated with opioid analgesics and who undergo 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 |

Symptoms: Serious overdosage with opioids may be characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme

somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

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 opioids. An appropriate dose of the antagonist 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 opioids, 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 individuals 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 formulation has been taken.

## DOSAGE AND ADMINISTRATION

**Codeine Contin® (codeine controlled release tablets) tablets should be swallowed whole and should not be chewed, dissolved or crushed. Taking broken, chewed, dissolved or crushed tablets could lead to rapid release and absorption of a potentially fatal dose of codeine. All strengths may be halved, except 50 mg. The half tablets should also be swallowed intact.**

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

**Doses of Codeine Contin are expressed as codeine base. Codeine phosphate formulations contain approximately 75% codeine base. Patients currently receiving oral immediate release formulations of plain codeine phosphate may be transferred to Codeine Contin at an approximately 25% lower total daily codeine dosage, equally divided into two 12 hourly Codeine Contin doses.**

For patients who are currently receiving analgesic combinations of codeine phosphate and acetaminophen or A.S.A., Table 1 provides a guide to the recommended initial and maintenance doses of **Codeine Contin**.

**TABLE 1**
**CONVERSION FROM ACETAMINOPHEN (OR ASA)**
**PLUS CODEINE PHOSPHATE COMBINATIONS**

| Number of 30 mg Codeine Combination Tablets Per Day | Initial Dose of Codeine Contin | Maintenance Dose of Codeine Contin |
|---|---|---|
| 4 - 6 | 50 mg q12h | 100 mg q12h |
| 7 - 9 | 100 mg q12h | 150 mg q12h |
| 10 - 12 | 150 mg q12h | 200 mg q12h |
| >12 | 200 mg q12h | as needed (maximum 300 mg q12h) |

Patients with pain who are not currently receiving other opioid analgesics, or who are receiving fewer than four tablets per day of a codeine combination preparation, should be initiated at a dose of 50 mg **Codeine Contin** every 12 hours and the dose titrated as needed.

For patients who are receiving an alternate opioid, the "oral codeine phosphate equivalent" of the analgesic presently being used should be determined. Having determined the total daily dosage of the present analgesic, Table 2 can be used to calculate the approximate daily oral codeine phosphate dosage that should provide equivalent analgesia. An approximately 25% lower dose of **Codeine Contin** should then be prescribed, equally divided into two 12 hourly doses.

Dose Titration: Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the patient's pain should aim at regular**

**administration of the lowest dose of controlled release codeine (Codeine Contin) which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response. In patients receiving **Codeine Contin** chronically, the dose should be titrated at intervals of 48 hours to that which provides satisfactory pain relief without unmanageable side effects. Doses of **Codeine Contin** above 300 mg q12h have not been extensively studied, and above these levels it is preferable that patients be transferred to an opioid such as morphine, which is recommended for severe pain. **Codeine Contin** is designed to allow 12 hourly dosing.

**If breakthrough pain repeatedly occurs at the end of the dosing interval it is generally an indication for a dosage increase rather than more frequent administration of controlled release codeine (Codeine Contin).**

Adjustment or Reduction of Dosage: Following successful relief of 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 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 suffering from some of these forms of chronic pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

Management of Breakthrough Pain: For patients whose dose has been titrated to the recommended maintenance dose, without attainment of adequate analgesia, the total daily dose may be increased, unless precluded by side effects. If breakthrough pain persists despite appropriate adjustments of **Codeine Contin** dose, plain acetaminophen may be given (325-650 mg q4-6h p.r.n. to a maximum of 4,000 mg/24 hours). If immediate release codeine phosphate preparations or acetaminophen plus codeine phosphate combination analgesics (q4-6h p.r.n.) are used for breakthrough pain, the doses of codeine phosphate* are 15, 30, 45, 60, 90 mg for patients receiving **Codeine Contin** 100, 200, 300, 400, 600 mg/day, respectively.

(*based on a rescue dose of codeine base which should not exceed 1/8 of the daily dose of **Codeine Contin**.)

**TABLE 2**
**OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]**

| Drug | Equivalent Dose (mg)[2] (compared to morphine 10 mg IM) | | Duration of Action (hours) |
|---|---|---|---|
| | Parenteral | Oral | |
| **Strong Opioid Agonists:** | | | |
| Morphine | 10 | 60[3] | 3-4 |
| Oxycodone | 15 | 30[4] | 2-4 |
| Hydromorphone | 1.5 | 7.5 | 2-4 |
| Anileridine | 25 | 75 | 2-3 |
| Levorphanol | 2 | 4 | 4-8 |
| Meperidine[6] | 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 |
| Propoxyphene | 50 | 100 | 2-4 |
| **Mixed Agonist-Antagonists[7]:** | | | |
| Pentazocine[6] | 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 the data were 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] Based on single entity oral oxycodone in acute pain.

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

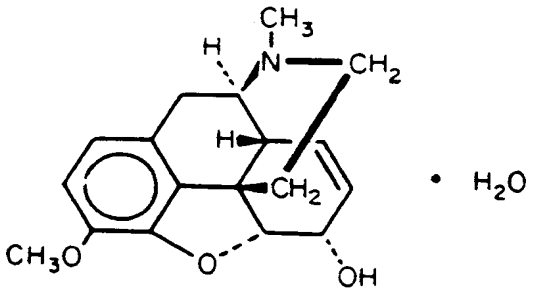
[6] Not recommended for the management of chronic pain.

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

## PHARMACEUTICAL INFORMATION

Proper Name: Codeine Monohydrate

Structure:




Molecular Formula: $C_{18}H_{21}NO_3 \bullet H_2O$

Chemical Name: 7, 8-Didehydro-4, 5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol monohydrate

Molecular Weight: 317.38

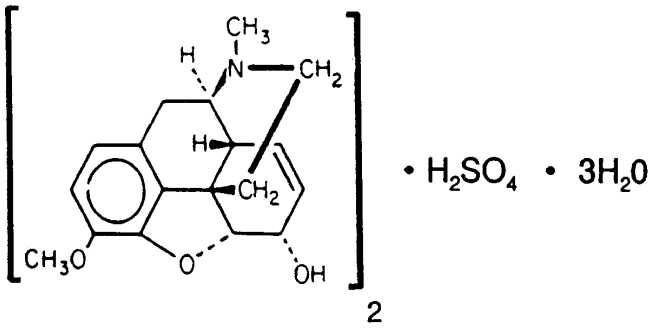
Appearance: Colourless or white crystals or white, crystalline powder.

Solubility: Slightly soluble in water, very soluble in chloroform and freely soluble in ether.

Melting Point: 154° - 158°C.

Proper Name: Codeine Sulfate Trihydrate

Structure:




Molecular Formula: $(C_{18}H_{21}NO_3)_2 \bullet H_2SO_4 \bullet 3H_20$

Chemical Name: 7, 8-Didehydro-4, 5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol sulfate trihydrate

Molecular Weight: 750.87

Appearance: White crystals or white, crystalline powder.

Solubility: Slightly soluble in water, freely soluble in water at 80°C, very slightly soluble in alcohol, insoluble in chloroform and in ether.

Melting Point: 278°C (anhydrous)

**Composition:**

Active Ingredient(s): Codeine

Non-medicinal Ingredients *(all strengths)*: hydroxyethyl cellulose, lactose, magnesium stearate, stearyl alcohol and talc

***50 mg Film Coating:*** Opadry Blue Y-5-10544

- FD&C Blue No. 2 Aluminum Lake
- hydroxypropyl cellulose
- hydroxypropyl methylcellulose
- polyethylene glycol
- titanium dioxide

***100 mg Film Coating:*** Opadry Yellow Y-5-2036

- D&C Yellow No. 10 Aluminum Lake
- FD&C Yellow No. 5 Aluminum Lake
- hydroxypropyl cellulose
- hydroxypropyl methylcellulose
- polyethylene glycol
- titanium dioxide

***150 mg Film Coating:*** Opadry Red Y-5-1842

- FD&C Yellow No. 6 Aluminum Lake
- FD&C Red No. 40 Aluminum Lake
- hydroxypropyl cellulose
- hydroxypropyl methylcellulose
- polyethylene glycol
- titanium dioxide

***200 mg Film Coating:*** Opadry Orange Y-5-2467

- FD&C Yellow No. 6 Aluminum Lake
- hydroxypropyl cellulose
- hydroxypropyl methylcellulose
- polyethylene glycol
- titanium dioxide

**Stability and Storage Recommendations:** Store at room temperature (15° - 30°C).

## AVAILABILITY OF DOSAGE FORMS

**Codeine Contin®** (codeine controlled release tablets) are available in 50 mg (blue), 100 mg (yellow), 150 mg (red) and 200 mg (orange) strengths. **Codeine Contin** 50 mg tablets contain 26.5 mg of codeine monohydrate and 31.35 mg of codeine sulfate trihydrate (each equivalent to 25 mg codeine anhydrous). **Codeine Contin** 100 mg tablets contain 53 mg of codeine monohydrate

and 62.7 mg of codeine sulfate trihydrate (each equivalent to 50 mg codeine anhydrous). **Codeine Contin** 150 mg tablets contain 79.5 mg of codeine monohydrate and 94.1 mg of codeine sulfate trihydrate (each equivalent to 75 mg codeine anhydrous). **Codeine Contin** 200 mg tablets contain 106 mg of codeine monohydrate and 125.4 mg of codeine sulfate trihydrate (each equivalent to 100 mg codeine anhydrous).

The tablets are film-coated with the following appearance:

50 mg - Blue, round, film coated tablets with PF imprinted on one side and CC 50 on the other side.

100 mg - Yellow, round, scored film coated tablets with PF imprinted on one side and CC 100 on the other side.

150 mg - Red, round, scored film coated tablets with PF imprinted on one side and CC 150 on the other side.

200 mg - Orange, caplet shaped, scored film coated tablets with PF imprinted on one side and CC 200 on the other side.

Supplied in opaque, plastic bottles containing 60 tablets.

## INFORMATION FOR THE CONSUMER

**Read this information carefully before you take Codeine Contin® 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 **Codeine Contin** is right for you. Share the information in this leaflet with members of your household.

### What is codeine?

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

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

### What is Codeine Contin?

**Codeine Contin** is a controlled release tablet containing the medicine codeine. **Codeine Contin** is made to slowly release codeine over a 12 hour period, and requires a dose every 12 hours to control your pain. **Codeine Contin** is used to treat mild to moderate pain requiring the prolonged use of an opioid analgesic preparation. **Codeine Contin** tablets are available in four strengths: 50 mg (blue), 100 mg (yellow), 150 mg (red) and 200 mg (orange). It may be necessary for you to take more than

one tablet strength (different coloured tablets) at the same time in order to receive the total daily dosage prescribed by your doctor.

**Before you take Codeine Contin:**

Your doctor should know about all of your medical conditions before deciding if **Codeine Contin** is right for you and what daily dosage is best. Tell your doctor about all of your medical problems, especially the following ones: difficulty breathing, asthma or other chronic 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.

**Codeine Contin** should not be used if:

- your doctor did not prescribe it for you;
- your pain can be controlled by occasional use of other painkillers;
- you have severe asthma or severe lung problems;
- you are allergic to codeine or opioids;
- you suffer from alcoholism;
- you have a head injury;
- you suffer from seizures;
- you are at risk of blocked intestines;
- you had surgery less than 24 hours ago;

- you are pregnant or intend to become pregnant;
- you are breast-feeding. Codeine may cause harm to a breastfed baby.

**How to take Codeine Contin:**

**Codeine Contin tablets must be swallowed whole and should not be chewed, dissolved or crushed, since this can cause the release of too much codeine that can seriously harm you. All strengths may be halved, except the 50 mg. Codeine Contin 100, 150 and 200 mg tablets have a score line to facilitate halving, if directed by your doctor. The half tablets should also be swallowed intact.**

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

Follow your doctor's directions exactly. **Codeine 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 **Codeine Contin**.

Your daily dosage of **Codeine 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 **Codeine Contin**. Be sure to use **Codeine Contin** only for the condition for which it was prescribed.

**Stopping Codeine Contin:**

Consult your doctor for instructions on how to discontinue taking **Codeine Contin**. You should not stop taking **Codeine 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 **Codeine Contin** you should take the unused tablets to your pharmacist to be destroyed.

**Side effects you may have while taking Codeine 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 **Codeine 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.

If you are a nursing mother taking codeine, call your doctor if you become extremely sleepy and have trouble caring for your baby.

Breastfed babies usually nurse every two to three hours and should not sleep more than four hours at a time. If your baby shows signs of more than usual increased sleepiness, difficulty breast-feeding, breathing difficulties, or limpness, talk to the baby's doctor immediately. If you cannot reach the doctor right away, take the baby to an emergency room.

**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 if you don't feel sick.

**Taking Codeine Contin with other medications:**

You should not take **Codeine 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 **Codeine Contin** with other medicines. These include:

- other opioids, anaesthetics, sedatives, tranquilizers, hypnotics, barbiturates, phenothiazines, amphetamines, chlorpromazine, methocarbamol, some heart medications (e.g., beta-blockers), blood-thinners (coumarin or other anticoagulants), chloral hydrate and glutethimide (not

available in Canada);

- sedating antihistamines, depressants, alcoholic beverages 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 **Codeine 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 **Codeine Contin.**

Patients who have taken **Codeine 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 Codeine Contin:**

A new written prescription is required from your doctor each time you need more **Codeine 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 **Codeine Contin** from any other doctor - unless responsibility for your pain management has been transferred to another doctor.

Consult your doctor if you feel sedated or drowsy, confused, have shallow breathing, or have severe constipation. Should your pain increase or any other complaint develop as a result of taking **Codeine Contin,** tell your doctor immediately.

**Storage of Codeine Contin:**

**Codeine Contin** contains an opioid medicine and must be stored in a secure place to prevent theft and misuse. Do not give **Codeine Contin** to anyone other than the person for whom it was prescribed since it may seriously harm them. Keep **Codeine Contin** out of the sight and reach of children. Accidental overdose by a child is dangerous and may result in death.

This preparation contains codeine and should not be administered to children.

Keep **Codeine Contin** in a dry place, between 15° and 30°C.

This leaflet summarizes important information about **Codeine 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.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789**
  - **Mail to: Canada Vigilance Program**
    **Health Canada**
    **Postal Locator 0701E**
    **Ottawa, ON K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available in the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

*NOTE: Should you require information related to the management of the side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## PHARMACOLOGY

Pharmacodynamics: Codeine and related opioids produce their major effects on the CNS and bowel by acting as agonists at specific saturable opioid receptors in the CNS and other tissues, particularly at the mu receptors. The mechanism of action of opioids for analgesia is not at peripheral loci but rather at the level of the spinal cord and higher nerve centers where they are thought to alter the transmission of nerve impulses. The antitussive properties of codeine may be exerted not through the mu receptors but other receptors that are not naloxone sensitive.

It has been speculated that the analgesic effectiveness of codeine is mediated partially by morphine, which is a metabolite of codeine. However, recent studies identifying endogenous formation of codeine and binding of codeine and its metabolites to mu receptors are supportive of an analgesic effect of codeine itself.

Codeine and other opioids act on the brain stem respiratory centers reducing their responsiveness to increases in carbon dioxide tension, resulting in respiratory depression.

Nausea and vomiting are primarily the result of opioid stimulation of the chemoreceptor trigger zone in the area postrema of the medulla, although stimulation of the vestibular apparatus and delayed gastric emptying may play a contributory role.

The effect of opioids on cardiac function is negligible. However, peripheral vasodilation may result in lightheadedness, dizziness and fainting in ambulatory patients. The increased histamine release

stimulated by opioids may also be responsible for this hypotension. Histamine release may cause dilation of cutaneous blood vessels resulting in the skin feeling flushed and warm. Pruritus and sweating frequently follow codeine administration and may be a reaction to the release of histamine. Pruritus may also be due to activation of neural systems as opioids that do not release histamine also cause pruritus.

The primary action of codeine-like drugs on the gastrointestinal system is a decrease in motility: propulsive contractions in the small intestine are decreased, and propulsive peristaltic waves in the colon are either diminished or abolished. This accounts for the frequently observed side effect of constipation following opioid administration. The mechanism of action by which this occurs is probably a combination of both local effects on the intestine as well as on CNS centers regulating intestinal motility.

## TOXICOLOGY

Animal: The $LD_{50}$ of oral codeine in mice and rats, as determined by 15 different investigators, was between 237-640 mg/kg. Animal studies with a number of opioids, including codeine, have indicated the possibility of teratogenic effect. No adequate long-term studies have been conducted in animals to determine whether codeine has a potential for carcinogenesis.

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

## REFERENCES

1. Arkinstall W, Sandler A, Goughnour B, Babul N, Harsanyi Z, Darke AC. Efficacy of controlled release codeine in chronic nonmalignant pain: A randomized, placebo-controlled clinical trial. Pain 1995;62:169-78.

2. Band CJ, Band PR, Deschamps M, Besner J-G, Coldman AJ. Human pharmacokinetic study of immediate-release (codeine phosphate) and sustained-release (Codeine Contin) codeine. J Clin Pharmacol 1994;34:938-43.

3. Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. J Pharmacol Exp Ther 1978;207(1):92-100.

4. Chary S, Goughnour BR, Moulin DE, Thorpe WR, Harsanyi Z, Darke AC. The dose-response relationship of controlled-release codeine (Codeine Contin) in chronic cancer pain. J Pain Symptom Manage 1994;9:363-71.

5. Chau TT, Carter FE, Harris LS. 3H-Codeine binding in the guinea pig lower brain stem. Pharmacology 1982; 25:12-17.

6. Eddy NB, Friebel H, Hahn K, Halbach H. Codeine and its alternates for pain and cough relief. Bull WHO 1968;38:673-741.

7. Dhaliwal HS, Sloan P, Arkinstall WW, Thirlwell MP, Babul N, Harsanyi Z, et al. Randomized evaluation of controlled-release codeine and placebo in chronic cancer pain. J Pain Symptom Manage 1995;10:612-23.

8. Findlay JWA, Butz RF, Welch RM. Specific radioimmunoassays for codeine and morphine. Metabolism of codeine to morphine in the rat. Res Commun Chem Pathol Pharmacol 1977;17(4):595-603.

9. Findlay JWA, Butz RF, Welch RM. Codeine kinetics as determined by radioimmunoassay. Clin Pharmacol Ther 1977;22(4):439-46.

10. Findlay JWA, Jones EC, Butz RF, Welch RM. Plasma codeine and morphine concentrations after therapeutic oral doses of codeine-containing analgesics. Clin Pharmacol Ther 1978;24(1):60-8.

11. Guay DRP, Awni WM, Halstenson CE, Findlay JW, Opsahl JA, Abraham PA, et al. Pharmacokinetics of codeine after single-and multiple-oral-dose administration to normal volunteers. J Clin Pharmacol 1987;27:983-7.

12. Hull JH, Findlay JW, Rogers JF, Welch RM, Butz RF, Bustrack JA. An evaluation of the effects of smoking on codeine pharmacokinetics and bioavailability in normal human volunteers. Drug Intell Clin Pharm 1982;16:849-50.

13. Jaffe JH, Martin WR. Narcotic analgesics and antagonists. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics, 5th ed, New York: Macmillan Press, 1975:245.

14. Kay DC, Gorodetzky CW, Martin WR. Comparative effects of codeine and morphine in man. J Pharmacol Exp Ther 1967;156(1):101-6.

15. Portenoy RK. Chronic opioid therapy in non-malignant pain. J Pain Symptom Manage 1990;5:S46-S62.

16. Portenoy RK, Foley KM, Inturissi CE. The nature of opioid responsiveness and its implication for neuropathic pain: New hypotheses derived from studies of opioid infusions. Pain 1990;43:273-86.

17. Portenoy RK. Cancer Pain: Pathophysiology and syndromes. Lancet 1992;339:1026-31.

18. The Purdue Frederick Company. A crossover bioavailability study of Codeine Contin 100 mg tablets and codeine sulfate tablets 60 mg immediate release tablets. Final study report. Norwalk, CT: Medical Department; February 20, 1986. Report No.: CC82-1001. Conducted by: Biodecision Laboratories; Pittsburgh, PA, 1986. Data on file.

19. The Purdue Frederick Company. A cross-over bioavailability study of single dose comparison of Codeine Contin 100 mg tablets and codeine phosphate 60 mg liquid. Final study report. Norwalk, CT: Medical Department; April 25, 1986. Report No.: CC83-0705. Conducted by: Biodecision Laboratories; Pittsburgh, PA, 1986. Data on file.

20. The Purdue Frederick Company. Steady-state bioavailability of one Codeine Contin 100 mg tablet q12h and 50 mg immediate release codeine phosphate solution, q6h. Final study report. Norwalk, CT: Medical Department; October 11, 1990. Report No.: CC86-0205. Conducted by: Phamaco Dynamics Research Inc.; Austin TX, 1990. Data on File.

21. The Purdue Frederick Company. A comparative randomized bioavailability study of one Codeine Contin 100 mg tablet, one Codeine Contin 150 mg tablet and one 200 mg Codeine Contin tablet relative to 100 mg of immediate-release Codeine Contin liquid in normal volunteers. Final study report. Norwalk, CT: Medical Department; December 7, 1988. Report No.: CC86-0606. Data on File.

22. The Purdue Frederick Company. A single dose randomized crossover bioavailability study of one Codeine Contin 100 mg tablet in fed vs. fasted subjects. Final study report. Norwalk, CT: Medical Department; April 20, 1989. Report No.: CC86-0902. Data on File.

23. The Purdue Frederick Company. Double-blind, randomized, single dose, parallel group study to assess the analgesic efficacy and safety of Codeine Contin, acetaminophen with codeine and placebo in pain due to oral surgery. Final study report. Norwalk, CT: Medical Department; January 30, 1990. Report No.: CC87-0103. Data on File.

24. The Purdue Frederick Company. A pilot study to determine the comparative analgesic efficacy of Trilisate, Trilisate with Codeine Contin, and Phenaphen with Codeine No.3, in patients with postsurgical dental pain. Final study report. Norwalk, CT: Medical Department; December 12, 1988. Report No.: CC88-0501. Data on File.

25. The Purdue Frederick Company. Double-blind comparative study evaluating the safety and analgesic efficacy of controlled-release codeine (Codeine Contin tablets) given twice a day with prn supplements of acetaminophen and acetaminophen with codeine given as needed in patients with stable mild to moderately severe low back pain. Final study report. Norwalk, CT: Medical Department; March 2, 1994. Report No.: CC90-1107. Data on File.

26. The Purdue Frederick Company. A single-dose, four-way, crossover bioavailability study of one (1) controlled-release codeine 100 mg tablet formulation with and without food and codeine phosphate liquid 100 mg with and without food. Final study report. Norwalk, CT: Medical Department; December 16, 1993. Report No.: CC91-0304. Data on File.

27. Quiding H, Oikarinen V, Sane J, Sjõblad A-M. Analgesic efficacy after single and repeated doses of codeine and acetaminophen. J Clin Pharmacol 1984;24:27-34.

28. Quiding H, Anderson P, Bondesson U, Boréus LO, Hynning P-Å. Plasma concentrations of codeine and its metabolite, morphine, after single and repeated oral administration. Eur J Clin Pharmacol 1986;30:673-7.

29. Quiding H, Lundqvist G, Boreus LO, Bondesson U, Ohrvik J. Analgesic effect and plasma concentrations of codeine and morphine after two dose levels of codeine following oral surgery. Eur J Clin Pharmacol 1993;44:319-23.

30. Scott JF, ed. Cancer Pain: A Monograph on the Management of Cancer Pain: Ministry of Supply and Services Canada. 1984 Cat. No. H42-2/5-1984E.

31. Sunshine A, Laska EM, Olsen NZ. Analgesic effects of oral oxycodone and codeine in the treatment of patients with postoperative, postfracture, or somatic pain. In: Foley KM and Inturrisi CE., eds. Advances in pain research and therapy. Vol. 8. Raven Press, New York, 1986;225-34.