

Codeine Contin®

Codeine Monohydrate—Codeine Sulfate Trihydrate Opioid Analgesic

Purdue Pharma

Pharmacology: 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 centre to CO₂, 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 i.m. codeine in terms of total analgesia. The relative potency of i.m. codeine phosphate is approximately that of i.m. morphine sulfate and orally, 200 mg of codeine phosphate is equivalent to 20 to 30 mg of morphine sulfate during chronic dosing.

The analgesic efficacy of codeine controlled release has been evaluated in multiple dose studies in patients with cancer pain and chronic nonmalignant 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 nonmalignant pain receiving q4h prn 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 prn plain acetaminophen, produced lower pain scores and less fluctuation in pain throughout the day than prn acetaminophen plus codeine.

Pharmacokinetics: Codeine is readily absorbed from the gastrointestinal tract and has an oral bioavailability of 53%, relative to the i.m. 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.

Codeine controlled release 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 controlled release is not significantly increased, but peak concentrations are somewhat delayed, occurring at 3.9 to 4.5 hours postdose.

Indications: For the relief of mild to moderate pain requiring the prolonged use of an opioid analgesic preparation.

Contraindications: Patients with 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).

Warnings: 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 controlled release 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 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 anesthetics, 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 controlled release within 24 hours of the procedure.

Pregnancy: Animal studies with a number of opioids, including codeine, have indicated the possibility of teratogenic effects. In humans, it is not known whether codeine can cause fetal harm when administered during pregnancy or can affect reproductive capacity. Since codeine crosses the placental barrier, codeine controlled release should be given to pregnant patients only when the anticipated benefits outweigh the risks to the fetus.

Precautions:

General: 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.

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 centre, and the respiratory depressant effects of codeine may reduce respiratory drive to the point of apnea.

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 anesthetics.

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.

Pregnancy: Labor/Delivery: Codeine crosses the placental barrier and its administration during labor can produce respiratory depression in the neonate.

Lactation: Codeine has been detected in human breast milk. Caution should be exercised if codeine is administered to a nursing mother.

Occupational Hazards: 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, anesthetics, sedatives, hypnotics, barbiturates, phenothiazines, chloral hydrate and glutethimide may enhance the depressant effects of codeine. MAO inhibitors (including procarbazine HCl), 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.

Adverse Effects: Adverse effects of codeine controlled release 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 CNS depression and, to a lesser degree, circulatory depression.

Most Common Adverse Effects Requiring Medical Attention: The most frequently observed side effects of opioid analgesics such as codeine are sedation, nausea and vomiting, constipation, lightheadedness, dizziness, and sweating.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naive 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 3 to 5 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 3 or 4 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: Dysphoria, euphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), muscle rigidity, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis, transient hallucinations and disorientation, visual disturbances, insomnia and increased intracranial pressure may occur.

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

Respiratory: bronchospasm and laryngospasm.

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

Genitourinary: urinary retention or hesitancy and antidiuretic effects

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

Withdrawal (Abstinence) Syndrome: Physical dependence with or without psychological dependence tends to occur on 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, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal from the drug, these symptoms are usually mild.

Overdose:

For management of a suspected drug overdose, CPhA recommends that you contact your **regional Poison Control Centre**. See the *CPS* Directory section for a list of .

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 HCl 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 i.v. 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, i.v. 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: 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 receiving analgesic combinations of codeine phosphate and acetaminophen or ASA, Table 1 provides a guide to the recommended initial and maintenance doses of Codeine Contin.

**Table 1: Codeine Contin
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 4 tablets/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.

Codeine Contin tablets should not be chewed or crushed. All strengths may be halved except 50 mg.

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 the regular administration of the lowest dose which will maintain the patient free of pain at all times.** Dosage adjustments should be based on the patient's clinical response. In patients receiving codeine controlled release 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 controlled release above 300 mg every 12 hours 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 controlled release 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.**

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.

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 controlled release dose, plain acetaminophen may be given (325 to 650 mg every 4 to 6 hours prn to a maximum of 4 000 mg/24 hours). If immediate release codeine phosphate preparations or acetaminophen plus codeine phosphate combination analgesics (every 4 to 6 hours prn) are used for breakthrough pain, the doses of codeine phosphate (based on a rescue dose of codeine base which should not exceed 1/4 of the daily dose of Codeine Contin) are 15, 30, 45, 60, 90 mg for patients receiving Codeine Contin 100, 200, 300, 400, 600 mg/day, respectively.

Table 2: Codeine Contin

Opioid Analgesics: Approximate Analgesic Equivalences^a

Drug	Equivalent Dose (mg) ^b (compared to morphine 10 mg i.m.)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists			
Morphine	10	60 ^c	3-4
Oxycodone	15	30 ^d	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine ^e	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone ^e	—	—	—
Heroin	5-8	10-15	3-4
Weak Opioid Agonists			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists^e			

Drug	Equivalent Dose (mg) ^b (compared to morphine 10 mg i.m.)		Duration of Action (hours)
	Parenteral	Oral	
Pentazocine ^f	60	180	3–4
Nalbuphine	10	—	3–6
Butorphanol	2	—	3–4

^a 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. 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.

^b 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.

^c 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 to 3:1 (i.e., 20 to 30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).

^d Based on single entity oral oxycodone in acute pain.

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

^f Not recommended for the management of chronic pain.

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

Information for the Patient:

Supplied: 50 mg: Each blue, round, film-coated tablet, with PF printed on one side and CC 50 on the other side, contains: codeine monohydrate 26.5 mg and codeine sulfate trihydrate 31.35 mg (each equivalent to codeine anhydrous 25 mg). Nonmedicinal ingredients: FD&C Blue #2 aluminum lake, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, propylene glycol, stearyl alcohol, talc and titanium dioxide. Opaque, high density polyethylene bottles of 50.

100 mg: Each yellow, round, scored, film-coated tablet, with PF imprinted on one side and CC 100 on the other side, contains: codeine monohydrate 53 mg and codeine sulfate trihydrate 62.7 mg (each equivalent to codeine anhydrous 50 mg). Nonmedicinal ingredients: D&C Yellow #10 aluminum lake, FD&C Yellow #5 aluminum lake, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, propylene glycol, stearyl alcohol, talc and titanium dioxide. Opaque, high density polyethylene bottles of 50.

150 mg: Each red, round, scored, film-coated tablet, with PF imprinted on one side and CC 150 on the other side, contains: codeine monohydrate 79.5 mg and codeine sulfate trihydrate 94.1 mg (each equivalent to codeine anhydrous 75 mg). Nonmedicinal ingredients: FD&C Yellow #6 aluminum lake, FD&C Red #40 aluminum lake, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, propylene glycol, stearyl alcohol, talc and titanium dioxide. Opaque, high density polyethylene bottles of 50.

200 mg: Each orange, caplet-shaped, scored, film-coated tablet, with PF imprinted on one side and CC 200 on the other side, contains: codeine monohydrate 106 mg and codeine sulfate trihydrate 125.4 mg (each equivalent to codeine anhydrous 100 mg). Nonmedicinal ingredients: FD&C Yellow #6 aluminum lake, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, propylene glycol, stearyl alcohol, talc and titanium dioxide. Opaque, high density polyethylene bottles of 50.

Store at 15 to 30°C.

(Shown in Product Identification Section)