PRESCRIBING INFORMATION

[N]ACET-CODEINE 30

[N]ACET-CODEINE 60

(Acetaminophen and Codeine Phosphate Tablets, USP)

300 mg/30 mg

300 mg/60 mg

Analgesic-Antipyretic

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Date of Revision:
April 16, 2014

Submission Control No.: 172009

PRESCRIBING INFORMATION

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Acetaminophen and Codeine Phosphate Tablets, USP

Analgesic-Antipyretic

CLINICAL PHARMACOLOGY

Acetaminophen and codeine phosphate are analgesic, antipyretic agents.

ACTION

Acetaminophen, and codeine phosphate combine the analgesic effects of the centrally acting analgesic codeine, with a peripherally acting analgesic, acetaminophen.
Acetaminophen, and codeine phosphate are well absorbed orally.

Acetaminophen is distributed throughout most tissues of the body. Acetaminophen is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral potency of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10% of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Pharmacokinetics
Following oral administration of acetaminophen in combination with codeine, both drugs are rapidly absorbed with peak plasma levels occurring within 60 minutes.

The plasma elimination half-life ($t_{1/2}$) ranges from 1.5 to 3.5 hours for acetaminophen, and 1.5 to 4 hours for codeine. Metabolism is rapid; the principal metabolites are conjugates of glucuronic acid which are excreted in the urine. Less than 1% of an administered dose of codeine, and less than 4% of an administered dose of acetaminophen, is excreted unchanged in the urine.

INDICATIONS AND CLINICAL USE

ACET-CODEINE 30 is indicated for the relief of mild to moderate pain.

ACET-CODEINE 60 is indicated for the relief of moderate to severe pain.

Pediatrics
Regardless of clinical setting, the use of codeine, including ACET-CODIENE is not recommended in patients below the age of 12 years due to increased safety concerns (see WARNINGS AND PRECAUTIONS, Pediatrics).

CONTRAINDICATIONS

ACET-CODEINE (acetaminophen, and codeine phosphate) is contraindicated in:

- Patients who are hypersensitive to acetaminophen or codeine, asthma, convulsive states, pre-existing respiratory depression or embarrassment.
- Patients with severe hepatic impairment or severe active liver disease.
- In patients with known or suspected mechanical gastrointestinal obstruction (eg. Bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (eg. Ileus of any type).
- Patients with suspected surgical abdomen (eg. Acute appendicitis or pancreatitis).
- Patients with acute asthma or other obstructive airway, and status asthmaticus
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are pregnant, or during labour and delivery.
- Children under 12 years old.

WARNINGS AND PRECAUTIONS

As with any other non-prescription analgesic drug, physicians should be cognizant of and supervise the use of acetaminophen in patients with alcoholism, serious kidney or serious liver disease. Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports usually involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Physicians should alert their patients who regularly consume large amounts of alcohol not to exceed the recommended doses of acetaminophen.

Patients should be counselled to consult a physician if redness or swelling is present in an area of pain, if symptoms do not improve or if they worsen, or if new symptoms such as high fever, rash, itching, wheezing or persistent headache occur, as these may be signs of a condition which requires medical attention.

Acetaminophen should not be taken for pain for more than 5 days or for fever for more than 3 days, unless directed by a physician. As with any drug, patients who are pregnant or nursing a baby should consult a physician before taking this product.

Patients should be counselled not to use with other products containing acetaminophen. Patients should be counselled to consult a physician before use if they are taking tranquilizers, sedatives, sedating antihistamines or other depressants, 3 or more alcoholic beverages per day, natural health products, prescription drugs, salicylates, any other pain and fever relief medication or nonsteroidal anti-inflammatory drugs (NSAIDS).

Patients should be counselled to consult a physician before use if they have difficulty breathing, have asthma or other chronic lung disease.

Keep out of the sight and reach of children.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine produces dose-related respiratory depression. Caution should be exercised when acetaminophen with codeine is used postoperatively, in patients with pulmonary disease or shortness of breath or whenever ventilatory function is depressed.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Use with caution in patients with seizures as the seizures may be exacerbated or induced by opioids.

Codeine is habit forming and potentially abusable. Consequently, the extended use of this product is not recommended.

General

Acetaminophen and codeine phosphate tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

Respiratory

Codeine, including ACET-CODEINE, is not recommended for use in any patient in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, lung infections, multiple trauma or extensive surgical procedures.

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

labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform their patients about these risks and the signs of morphine overdose (see **WARNINGS AND PRECAUTIONS, Lactation**).

Lactation
Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. Because of the potential for serious adverse reactions in nursing infants from acetaminophen, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

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. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, **some women are ultra-rapid metabolizers of codeine (see WARNINGS and PRECAUTIONS, 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. 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 and Japanese, 0.5 to 1% in 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.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. 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. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding (see **WARNINGS AND PRECAUTIONS**, **Ultra-Rapid Metabolizers of Codeine**).

Hypersensitivity Reactions
Serious skin reactions
Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens – Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. It is important to recognize and react quickly to the initial symptoms of these reactions which may occur without warning but may be manifested by any serious skin reactions. Patients should be informed about the signs of serious reactions, and use of the drug should be discontinued at their first appearance.

Hepatic
Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories, etc.). Do not exceed the maximum recommended daily dose of acetaminophen (see **DOSAGE AND ADMINISTRATION**).

Occupational Hazards
Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks. Patients using this drug should be cautioned about driving a car or operating potentially hazardous machinery if they become drowsy or show impaired mental or physical abilities while taking this medication.

The patient should understand the single-dose and 24-hour dose limits, and the time interval between doses. Like other narcotic-containing medications, these drugs are subject to the Controlled Drugs and Substances Act.

Laboratory Tests
In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions
This drug may enhance the effects of other narcotic analgesics, alcohol, monoamine oxidase (MAO) inhibitors, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression. If such combined therapy is considered, the dose of 1 or both agents should be reduced and the benefits should be outweighed against the risk to the patient. This concurrent use of anticholinergic with codeine may produce paralytic ileus.

Patients who concomitantly medicate with warfarin-type anticoagulants and regular doses of acetaminophen have occasionally been reported to have unforeseen elevations in their international normalized ratio [INR]. Physicians should be cognizant of this potential interaction and monitor the INR in such patients closely while therapy is established. Many factors, including diet, medications, and environmental and physical states, may affect how a patient responds to anticoagulant therapy. There have been several reports that suggest that acetaminophen may produce hypoprothrombinemia (elevated INR or prothrombin time) when administered with coumarin derivatives. In other studies, prothrombin time did not change.

Reported changes have been generally of limited clinical significance, however, periodic evaluation of prothrombin time should be performed when these agents are administered concurrently.

In the period immediately following discharge from the hospital or whenever other medications are initiated, discontinued, or taken regularly, it is important to monitor patient response to anticoagulation therapy with additional prothrombin time of INR determinations.

Drug/Laboratory Test Interactions
Codeine may increase serum amylase levels.

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to whether acetaminophen or codeine have a potential for carcinogenesis or mutagenesis. No adequate studies have been conducted in animals to determine whether acetaminophen has a potential for impairment of fertility.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Use in Pregnancy

Teratogenic Effects:

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study, a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no adequate and well-controlled studies in pregnant women.

ACET-CODEINE (acetaminophen, and codeine phosphate) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects:

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.

Labour and Delivery:

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labour if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labour, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see **OVERDOSAGE**). The effects of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Children

These products contain codeine and should not be administered to children below the age of 12 years.

Drug Abuse and Dependence

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of acetaminophen and codeine phosphate. These drugs should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic- containing medications. Patients should be instructed to store ACET-CODIENE as for any medication, safely out of reach of children.

ADVERSE REACTIONS

The most frequently observed adverse effects include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, and vomiting. These effects seem to be more prominent in ambulatory patients than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, epigastric pain, abdominal pain, pruritus, rash, thrombocytopenia, and agranulocytosis. The incidence and severity of gastrointestinal upset is less than that after salicylate administration.

The classic gastrointestinal irritation associated with non-steroidal anti-inflammatory drugs, including ASA, does not occur with acetaminophen. Sensitivity reactions are rare and may manifest as rash or urticaria. Cross-reactivity in ASA-sensitive persons has been rarely reported. If sensitivity is suspected, discontinue use of the drug.

Patients who concomitantly medicate with warfarin-type anticoagulants and regular doses of acetaminophen have occasionally been reported to have unforeseen elevations in their INR. Physicians should be cognizant of this potential interaction and monitor the INR in such patients closely while therapy is established (see **WARNINGS AND PRECAUTIONS**, **Drug Interactions**).

At higher doses, codeine has most of the disadvantages of morphine, including respiratory depression.

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, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

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

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acetaminophen:

Typical Toxidrome: Significant overdoses of acetaminophen may result in potentially fatal hepatotoxicity. The physician should be mindful that there is no early presentation that is pathognomonic for the overdose. A high degree of clinical suspicion must always be maintained.

Due to the wide availability of acetaminophen, it is commonly involved in single and mixed drug overdose situations and the practitioner should have a low threshold for screening for its presence in a patient's serum. Acute toxicity after single dose overdoses of acetaminophen can be anticipated when the overdose exceeds 150 mg/kg. Chronic alcohol abusers, cachectic individuals, and persons taking pharmacologic inducers of the hepatic P450 microsomal enzyme system may be at risk with lower exposures. Chronic intoxication has rarely been reported in persons consuming in excess of 150 mg/kg of acetaminophen daily for several days.

Early symptoms following a hepatotoxic overdose may include nausea, vomiting, diaphoresis, lethargy, and general malise. If appropriate treatment is not instituted, these may progress to upper quadrant pain, confusion, stupor, and sequelae of hepatic necrosis, such as jaundice, coagulation defects, hypoglycemia, and encephalopathy. Renal failure and cardiomyopathy may also occur.

Specific Antidote: NAC (N-acetylcysteine) administered by either the intravenous or the oral route is known to be a highly effective antidote for acetaminophen poisoning. It is most effective when administered within 8 hours of a significant overdose but reports have indicated benefits to treatment initiated well beyond this time period. It is imperative to administer the antidote as early as possible in the time course of acute intoxication to reap the full benefits of the antidote's protective effects.

General Management: When the possibility of acetaminophen overdose exists, treatment should begin immediately and include appropriate decontamination of the GI tract, proper supportive care, careful assessment of appropriately timed serum acetaminophen estimations evaluated against the Matthew-Rumack nomogram, timely administration of NAC as required and appropriate follow-up care. Physicians unfamiliar with the current management of acetaminophen overdose should consult with a poison control centre immediately. Delays in initiation of appropriate therapy may jeopardize the patient's chances for full recovery.

Codeine:

Overdose of codeine 100 to 500 mg may cause a slow pulse, flush facies, kinetosis, and lassitude or excitement. Doses of 800 mg or more have caused prolonged miosis, muscular weakness, semiconsciousness, delirium, convulsions, rapid pulse, and finally circulatory collapse or respiratory paralysis. The human lethal dose for codeine is not known with certainty. Mortalities due to codeine appear to be quite unusual.

Typical Toxidrome: Narcotic/Opiate
Specific Antidote: Naloxone Hydrochloride.
The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdose of unusual sensitivity to narcotics. Therefore, an appropriate dose of this antagonist should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation.

General Management: Primary attention should be given to reestablishment of adequate exchange through provision of a patent airway and the institution of assisted or controlled ventilation. Stabilize the patient (A, B, C's), undertake appropriate gastrointestinal tract decontamination procedures, initiate supportive care, administer antidote as needed (see manufacturer's product monograph), consult with a Regional Poison Control Centre regarding ongoing management, and arrange for appropriate follow-up care.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

Do not co-administer with other drugs containing acetaminophen.

ACET-CODEINE should not be used in children less than 12 years old. Codeine, including ACET-CODEINE, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4 to 6 hours and not on scheduled intervals.

The maximum recommended dose of ACET-CODEINE should not be exceeded. Overdose may result in **severe or possibly fatal liver damage**.

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine, higher than 60 mg, fail to give commensurate relief of pain but merely prolong analgesia, and are associated with an appreciably increased incidence of undesirable side effects. Equivalently high doses in children would have similar effects.

ACET-CODEINE (acetaminophen, and codeine phosphate) tablets are given orally.

Dosage

ACET-CODEINE 30

Adults (≥ 12 years of age): 1 or 2 tablets every 4 to 6 hours, as required, or as directed by a physician. Do not exceed 12 tablets in 24 hours.

ACET-CODEINE 60

Adults (≥ 12 years of age): 1 tablet every 4 to 6 hours, as required, or as directed by a physician. Do not exceed 6 tablets in 24 hours.

Based on the dosage guidance, the number of tablets per dose and the maximum number of tablets per 24 hours should be conveyed in the prescription.

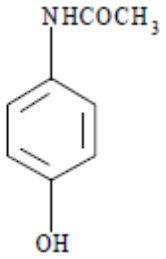
PHARMACEUTICAL INFORMATION

Drug substance:

Acetaminophen

Chemical Name: N-(4-hydroxyphenyl) acetamide

Structure:



Molecular Formula: $C_8H_9NO_2$

Molecular Weight: 151.2 g/Mol

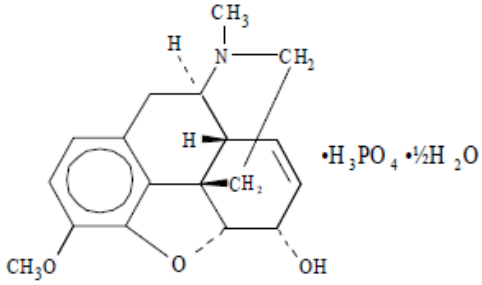
Physical property: white crystalline powder

Solubility: in boiling water 1 g/20 mL; in alcohol 1 g/10 mL

Codeine Phosphate

Chemical Name: 7, 8-didehydro-4,5α-epoxy-3- methoxy-17-methylmorphinan-6α-ol-phosphate(l:l) (salt) hemihydrate

Structure:



Molecular Formula: $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$

Molecular Weight: 406.4 g/mol

Physical Proprieties: white crystalline powder

Solubility: in water 4 g/mL; in alcohol 30 mg/10 mL

AVAILABILITY OF DOSAGE FORMS

ACET-CODEINE 30: each peach colored, round, flat, bevel edged tablet imprinted «ACET"» over a half score line with «30» in the middle & «CODEINE» under the half score on one side, and plain the other side, contain 300 mg of acetaminophen, 30 mg of codeine phosphate, and the following non-medicinal ingredients (in alphabetical order): colloidal silicon dioxide, croscarmellose sodium, FD & C Yellow #6 lake, magnesium stearate, microcrystalline cellulose, stearic acid.

Available in HDPE bottles of 100 and 500, and in blister packs of 4 x 25 tablets.

ACET-CODEINE 60: each white, round, flat, bevel edged tablet imprinted «ACET» over a half score line with «"60» in the middle & «CODEINE» under the half score on one side, and plain on the other side, contains 300 mg of acetaminophen, 60 mg of codeine phosphate, and the following non-medicinal ingredients (in alphabetical order): colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, stearic acid.

Available in HDPE bottles of 100 and 500, and in Blister packs of 4 x 25 tablets

Stability and Storage Recommendations:

Store between 15ºC and 30ºC in a tight, light-resistant container.

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REFERENCES

TYLENOL with Codeine No. 4 Prescribing Information, Janssen Inc., date of revision: July 5, 2013, control number 165413, 165416

Ratio-EMTEC-30 Prescribing Information, Teva Canada Limited., date of revision: June 25, 2013, control number: 165102