PRESCRIBING INFORMATION

[N]TYLENOL® No. 1

acetaminophen, caffeine and codeine phosphate caplets
300 mg acetaminophen, 15 mg caffeine and 8 mg codeine phosphate caplets

[N]TYLENOL® with Codeine No. 2

acetaminophen, caffeine and codeine phosphate tablets
300 mg acetaminophen, 15 mg caffeine and 15 mg codeine phosphate tablets

[N]TYLENOL® with Codeine No. 3

acetaminophen, caffeine and codeine phosphate tablets
300 mg acetaminophen, 15 mg caffeine and 30 mg codeine phosphate tablets

[N]TYLENOL® with Codeine No. 4

300 mg acetaminophen and 60 mg codeine phosphate tablets
acetaminophen and codeine phosphate tablets, USP

Analgesic-Antipyretic

NOT A PRODUCT MONOGRAPH

Janssen Inc.
200 Whitehall Drive
Markham, Ontario
L3R 0T5

McNeil Consumer Healthcare
Division of Johnson & Johnson Inc.

88 McNabb St.
Markham, Ontario
L3R 5L2

www.janssen.ca

DATE OF REVISION:
August 6, 2014

Submission Control No.: 174767, 174768, 175441, 175442

PRESCRIBING INFORMATION

[N]TYLENOL® No. 1
acetaminophen, caffeine and codeine phosphate caplets

[N]TYLENOL® with Codeine No. 2
[N]TYLENOL® with Codeine No. 3
acetaminophen, caffeine and codeine phosphate tablets

[N]TYLENOL® with Codeine No. 4
acetaminophen and codeine phosphate tablets, USP

Analgesic-Antipyretic

CLINICAL PHARMACOLOGY

TYLENOL® acetaminophen and codeine phosphate and TYLENOL® acetaminophen, caffeine and codeine phosphate are analgesic, antipyretic agents.

ACTION

TYLENOL® acetaminophen and codeine phosphate and TYLENOL® acetaminophen, caffeine and codeine phosphate combine the analgesic effects of the centrally acting analgesic codeine, with a peripherally acting analgesic, acetaminophen. Caffeine stimulates the central nervous system (CNS) at all levels including the cerebral cortex. In addition, it acts on the kidneys to produce mild diuresis, stimulates cardiac muscle, and depresses smooth muscle.

Acetaminophen, codeine phosphate and caffeine 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.

Caffeine is absorbed efficiently from the gastrointestinal tract, and peak plasma concentrations occur 15 to 120 minutes after ingestion. It is almost completely metabolized via oxidation, demethylation, and acetylation, with only about 1% of caffeine excreted via the urine. The principal metabolites in man are methyluric acid, 1-methylxanthine, paraxanthine, and theobromine.

Pharmacokinetics

Following oral administration of acetaminophen in combination with codeine, both drugs are rapidly absorbed with peak plasma levels occurring within 60 minutes. Given two tablets of TYLENOL® with Codeine No. 3, acetaminophen 600 mg produces a peak plasma level of 6.25 μg/mL within 40 minutes; codeine phosphate 60 mg produces a peak plasma level of 150 ng/mL within 60 minutes.

Following oral administration, caffeine is rapidly absorbed with a peak plasma level occurring within 15 to 120 minutes. Given an oral dose of 100 mg, peak plasma caffeine concentrations of 1.5 to 1.8 μg/mL are reached within 60 minutes.

The plasma elimination half-life ($t_{1/2}$) ranges from 1.5 to 3.5 hours for acetaminophen, 1.5 to 4 hours for codeine, and 2.5 to 4.5 hours for caffeine. 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 or caffeine and less than 4% of an administered dose of acetaminophen, is excreted unchanged in the urine.

INDICATIONS AND CLINICAL USE

TYLENOL® with Codeine No. 1, 2 and 3

TYLENOL® acetaminophen, caffeine and codeine phosphate tablets and caplets are indicated for the relief of mild to moderate pain associated with conditions such as headache, dental pain, myalgia, dysmenorrhea, pain following trauma, and pain following operative procedures. TYLENOL® acetaminophen, caffeine and codeine phosphate may also be effective in relieving the pain associated with various forms of arthritis, but is not indicated as primary therapy for rheumatoid arthritis and similar inflammatory conditions.

TYLENOL® with Codeine No. 4

TYLENOL® acetaminophen and codeine phosphate tablets are indicated for the relief of moderate to severe pain in adults only.

Pediatrics

Regardless of clinical setting, the use of codeine, including TYLENOL® with Codeine No.1, 2, 3 and 4, is not recommended in patients below the age of 12 years due to increased safety concerns (see **WARNINGS AND PRECAUTIONS, Pediatrics**).

CONTRAINDICATIONS

TYLENOL® with Codeine No. 2, No. 3, and No. 4 should not be administered to:

- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type)
- 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
- Women who are breastfeeding or during labour and delivery (see **WARNINGS AND PRECAUTIONS, Special Populations**)
- Children less than 12 years old

TYLENOL® with Codeine No. 1, 2, and 3 (acetaminophen, caffeine and codeine phosphate) should not be administered to patients who have previously exhibited hypersensitivity to caffeine, acetaminophen, codeine, or other opioids.

TYLENOL® with Codeine No. 4 (acetaminophen and codeine phosphate) should not be administered to patients who have previously exhibited hypersensitivity to acetaminophen, codeine or other opioids.

Codeine-containing products are contraindicated for postoperative pain management in children (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy.

WARNINGS AND PRECAUTIONS

General

As with any other non-prescription analgesic drug, physicians should be cognizant of and supervise the use of acetaminophen in patients with serious kidney or serious liver disease.

TYLENOL® with Codeine No. 2, 3, 4 are contraindicated in patients with acute alcoholism since 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.

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. Do not take continuously without medical review. Patients should be counselled to contact a physician if pain or fever persists or gets worse, or if new symptoms occur.

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, natural health products, prescription drugs, salicylates, any other pain and fever relief medication or nonsteroidal anti-inflammatory drugs (NSAIDS).

Keep out of the sight and reach of children.

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**.**

TYLENOL® with Codeine (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.

Codeine product should be discontinued at the earliest sign of toxicity and medical help should be sought as soon as possible.

Head Injury and Increased Intracranial Pressure

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

Codeine should be used with caution in patients at risk for additive CNS effects (see **DRUG INTERACTIONS**), convulsive disorders, head injuries, and in conditions in which intracranial pressure is raised.

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 have life-threatening or fatal respiratory depression or experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

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.

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**).

Respiratory depression and death have occurred in children who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine (see **Special Populations, Lactation**). Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine-containing products are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see **CONTRAINDICATIONS**).

Respiratory

Codeine, including TYLENOL® with Codeine No. 2, 3 and 4, 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.

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.

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

Gastrointestinal

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

Codeine should not be used in patients with obstructive bowel disorders and in patients at risk of paralytic ileus (see **CONTRAINDICATIONS**).

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**).

Advise your patients to seek medical attention as soon as an acetaminophen overdose is suspected. Advise them not to wait for symptoms to appear (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

Overdose Warning:
Taking more than the recommended dose (overdose) may cause liver damage. In case of overdose, get medical help right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

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 skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No adequate studies have been conducted in animals on 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.

Drug Abuse and Dependence
Codeine can produce drug dependence and has the potential for being abused. Tolerance, psychological and physical dependence may develop upon repeated administration of TYLENOL® acetaminophen and codeine phosphate, and TYLENOL® acetaminophen, caffeine and codeine phosphate. These drugs should be prescribed and administered with the same degree of caution appropriate to the use of other oral opioid medications. The extended use of these products is not recommended.

Special Populations

Use in Pregnancy

There are no adequate and well-controlled studies of the combination of codeine and acetaminophen in pregnant women.

TYLENOL® acetaminophen and codeine phosphate, and TYLENOL® acetaminophen, caffeine and codeine phosphate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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.

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.

Lactation

Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known.

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. 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.

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**).

Caffeine is distributed into the milk of nursing women.

Labour and Delivery:

Codeine

Opioid analgesics cross the placental barrier. Neonates who have been exposed to codeine in utero can develop withdrawal syndrome (neonatal abstinence syndrome) after delivery. Cerebral infarction has been reported in this setting.

The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn.

Acetaminophen

When given to the mother in labelled doses, acetaminophen crosses the placenta into fetal circulation as early as 30 minutes after ingestion and is effectively metabolized by fetal sulfate conjugation.

Pediatrics:

TYLENOL® with Codeine No. 1, 2, 3 and 4 contain codeine and should not be administered to children < 12 years of age.

Laboratory Tests

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

ADVERSE REACTIONS

The most frequently observed adverse effects include drowsiness, light-headedness, 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, 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 international normalized ratio (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** and **DRUG INTERACTIONS**).

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

Higher doses of caffeine lead to overstimulation of the higher centres of the CNS. Adverse CNS effects may include insomnia, restlessness, nervousness and mild delirium. Adverse gastrointestinal effects of caffeine may include nausea, vomiting, and gastric irritation. Although chronic administration of caffeine in animals has been associated with gastric ulceration, such a causal relationship in humans has not been adequately established to date.

DRUG INTERACTIONS

CNS depressants: Concomitant use with central nervous system depressants (e.g., barbiturates, chloral hydrate, benzodiazepines, phenothiazines, alcohol and centrally acting muscle relaxants) may cause additive CNS depression.

Opioid analgesics: Concurrent use with other opioid receptor agonists may cause additive CNS depression, respiratory depression and hypotensive effects.

CYP2D6 inhibitors: Codeine analgesia is believed to be dependent upon the cytochrome P450 isoenzyme CYP2D6 catalyzed o-demethylation to form the active metabolite morphine although other mechanisms have been cited. An interaction with quinidine, methadone, and paroxetine (CYP2D6 inhibitors) leading to decreased plasma concentrations of morphine has been described, which may have the potential to decrease codeine analgesia.

Warfarin-like compounds: 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In Case of Accidental Overdose: Call a Poison Control Centre or doctor immediately, even if you do not notice any signs or symptoms such as increased sweating, nausea, vomiting, stomach pain or loss of appetite.

Acetaminophen:

In adults and adolescents (≥ 12 years of age), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 grams over a period of 8 hours or less. Fatalities are infrequent (less than 3 to 4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children (< 12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity. Early symptoms following a potentially hepatotoxic overdose may include: anorexia, nausea, vomiting, diaphoresis, pallor and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Serious toxicity or fatalities have been extremely infrequent following an acute acetaminophen overdose in young children, possibly because of differences in the way they metabolize acetaminophen.

The following are clinical events associated with acetaminophen overdose that if seen with overdose are considered expected, including fatal events due to fulminant hepatic failure or its sequelae.

Table 1: Adverse Drug Reactions Identified with Overdose of Acetaminophen

Metabolism and Nutrition Disorders:
Anorexia
Gastrointestinal Disorders:
Vomiting, Nausea, Abdominal discomfort
Hepatobiliary Disorders:
Hepatic necrosis, Acute hepatic failure, Jaundice, Hepatomegaly, Liver tenderness
General Disorders and Administration Site Conditions:
Pallor, Hyperhidrosis, Malaise
Investigations:
Blood bilirubin increased, Hepatic enzymes increased, International normalized ratio increased, Prothrombin time prolonged, Blood phosphate increased, Blood lactate increased

The following clinical events are sequelae to acute hepatic failure and may be fatal. If these events occur in the setting of acute hepatic failure associated with acetaminophen overdose (adults and adolescents: ≥ 12 years of age: > 7.5 gm within 8 hours; children < 12 years of age: >150 mg/kg within 8 hours), they are considered expected.

Table 2: Expected Sequelae to Acute Hepatic Failure Associated with Acetaminophen Overdose

Infections and Infestations:
Sepsis, Fungal infection, Bacterial infection
Blood and Lymphatic System Disorders:
Disseminated intravascular coagulation, Coagulopathy, Thrombocytopenia

Metabolism and Nutrition Disorders:
Hypoglycemia, Hypophosphatemia, Metabolic acidosis, Lactic acidosis
Nervous System Disorders:
Coma (with massive acetaminophen overdose or multiple drug overdose), Encephalopathy, Brain edema
Cardiac Disorders:
Cardiomyopathy
Vascular Disorders:
Hypotension
Respiratory, Thoracic and Mediastinal Disorders:
Respiratory failure
Gastrointestinal Disorders:
Pancreatitis, Gastrointestinal hemorrhage
Renal and Urinary Disorders:
Acute renal failure
General Disorders and Administration Site Conditions:
Multi-organ failure

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.

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:
Risks of codeine overdose include asthenia, cardiorespiratory arrest, cerebral edema, coma,

confusional state, convulsion, drug dependence, fatigue, hypotension, hypoxia, ileus, miosis, renal failure, respiratory depression and respiratory failure, stupor, vomiting, and withdrawal syndrome.
Typical Toxidrome: Narcotic/Opiate
Specific Antidote: Naloxone HCl
General Management: 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.

Caffeine:
Typical Toxidrome: Xanthine (theophylline-like picture), CNS excitation, skeletal muscle irritability
Specific Antidote: None
General Management: Stabilize the patient (A, B, Cs), undertake appropriate gastrointestinal tract decontamination procedures, initiate supportive care, consult with a Regional Poison Control Centre regarding ongoing management, and arrange for appropriate follow-up care.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TYLENOL® with Codeine No. 1, 2, 3 and 4 should not be used in children less than 12 years old.

Codeine, including TYLENOL® with Codeine No. 2, 3 and 4, 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.

Do not co-administer with other drugs containing acetaminophen.

The maximum recommended dose of TYLENOL® should not be exceeded. Overdose may result in **severe or possibly fatal liver damage** (see **WARNINGS AND PRECAUTIONS, Hepatic**).

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.

TYLENOL® acetaminophen, caffeine and codeine phosphate tablets and caplets, as well as TYLENOL® acetaminophen and codeine phosphate tablets are given orally.

Dosage

TYLENOL® No. 1 caplets:
Adults (≥ 12 years of age):
Take 1 caplet every 4-6 hours, not to exceed 12 caplets in 24 hours. If pain does not respond to 1 caplet, take 2 caplets at next dose.

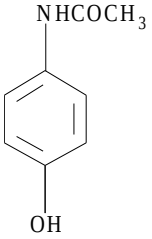
TYLENOL® with Codeine No. 2 and No. 3 tablets:
Adults (≥ 12 years of age):
Take 1 tablet every 4-6 hours as required, not to exceed 12 tablets in 24 hours. If pain does not respond to 1 tablet, take 2 tablets at next dose.

TYLENOL® with Codeine No. 4 tablets:
Adults (≥ 12 years of age):
Take 1 tablet every 4-6 hours as required, not to 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

The components of TYLENOL® acetaminophen and codeine phosphate dosage forms have the following structural formulae:

Acetaminophen

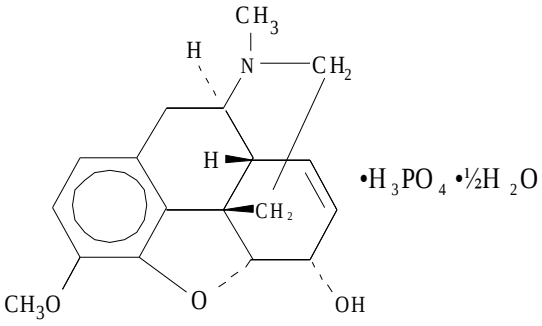


Chemical Name: N-(4-hydroxyphenyl) acetamide

Molecular Formula: $C_8H_9NO_2$

Molecular Weight: 151.2

Codeine Phosphate



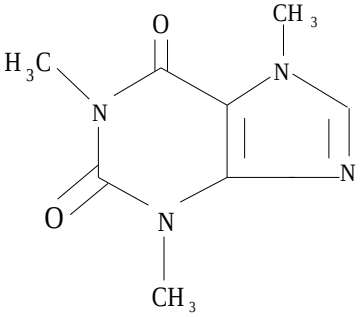
Chemical Name: 7, 8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol-phosphate(l:l) (salt) hemihydrate

Molecular Formula: $C_{18}H_{21}NO_3 \bullet H_3PO_4 \bullet ½H_2O$

Molecular Weight: 406.4

TYLENOL® acetaminophen, caffeine and codeine phosphate oral dosage forms have the additional component:

Caffeine



Chemical Name: 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione

Molecular Formula: $C_8H_{10}N_4O_2$

Molecular Weight: 194.2

Physical State:

Acetaminophen	-	white crystalline powder
Codeine phosphate	-	white crystalline powder
Caffeine	-	odourless silky white crystals

Solubility:

Acetaminophen	-	in boiling water 1 g/20 mL; in alcohol 1 g/10 mL
Codeine phosphate	-	in water 4 g/mL; in alcohol 30 mg/10 mL
Caffeine	-	in water 1 g/46 mL; in boiling water 1 g/1.5 mL; in alcohol 1 g/66 mL; in acetone 1 g/50 mL

General Product Stability:

Temperature	-	stable
Moisture	-	avoid excess moisture
Light	-	sensitive, protect from light

STORAGE AND STABILITY

Caplets No. 1: Store between 15-30ºC.
Tablets No. 2, No. 3, No. 4: Keep bottle tightly closed. Store at 15-30ºC.
Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TYLENOL® No. 1 caplets:

Each hard, white, capsule-shaped tablet imprinted with a stylized "M" and "McNEIL" on one face and imprinted with "NO. 1" on the other face, contains: acetaminophen 300 mg, caffeine 15 mg, and codeine phosphate 8 mg. Nonmedicinal ingredients: cellulose, cornstarch, magnesium stearate and sodium starch glycolate. Energy: 0.761 kJ (0.182 kcal). Sodium: <1 mmol (0.4 mg). Gluten-, lactose-, sodium metabisulphite- and tartrazine-free. Bottles of 30, 50, and 100 (supplied by McNeil Consumer Healthcare, Division of Johnson & Johnson Inc.).

TYLENOL® with Codeine No. 2 and No. 3 tablets:

Each round, hard, white tablet, flat-faced, bevelled, engraved with "2" or "3", respectively, on one side and with a flat-faced special design, bevelled, engraved with "McNEIL" on the other side, contains: acetaminophen 300 mg and caffeine 15 mg in combination with codeine phosphate 15 mg and 30 mg, respectively. Nonmedicinal ingredients: cellulose, microcrystalline cellulose, starch NF, sodium starch glycolate, pregelatinized starch, and magnesium stearate. Gluten-, lactose-, sodium metabisulphite- and tartrazine-free. Bottles of 500 (supplied by Janssen Inc.).

TYLENOL® with Codeine No. 4 tablets:

Each round, hard, white tablet, flat-faced, bevelled, engraved with "4" on one side and with a flat-faced special design, bevelled, engraved with "McNEIL" on the other side, contains: acetaminophen 300 mg and codeine phosphate 60 mg. Nonmedicinal ingredients: cellulose, cornstarch, magnesium stearate, sodium lauryl sulfate, sodium starch glycolate and talc. Energy: 1.704 kJ (0.405 kcal). Sodium: <1 mmol (0.6 mg). Gluten-, lactose-, sodium metabisulphite- and tartrazine-free. Bottles of 100 (supplied by Janssen Inc.).