ACETAMINOPHEN AND CODEINE PHOSPHATE- acetaminophen and codeine phosphate tablet
EPM Packaging Inc

Hepatotoxicity
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product.
WARNING: Death Related to Ultra-Rapid Metabolis m of Codeine to Morphine
Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

ACETAMINOPHEN AND CODEINE PHOSPHATE TABLETS, USP CIII
Rx only

Acetaminophen and codeine are supplied in tablet form for oral administration.
Acetaminophen, USP, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:
C H NO M.W. 151.16
Codeine phosphate, USP, 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate, a white crystalline powder, is a narcotic analgesic and antitussive. It has the following structural formula:
8 9 2
C H NO •H PO •1/2H O M.W. 406.37
Each tablet contains:
acetaminophen, USP.....300 mg
codeine phosphate, USP.....15 mg
(Warning: May be habit forming)
OR
acetaminophen, USP.....300 mg
codeine phosphate, USP..... 30 mg
(Warning: May be habit forming)
OR
acetaminophen, USP.....300 mg
codeine phosphate, USP..... 60 mg
(Warning: May be habit forming)
In addition, each tablet contains the following inactive ingredients: corn starch, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The 300 mg/60 mg strength tablets also contain crospovidone, povidone, pregelatinized starch, and stearic acid.
CLINICAL PHARMACOLOGY
This product combines the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen.
Pharmacokinetics
The behavior of the individual components is described below.
Codeine
Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain;

however, codeine is not bound to plasma proteins and does not accumulate in body tissues.
The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.
18 21 3 3 4 2
At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.
See OVERDOSAGE for toxicity information.
Acetaminophen
Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.
See OVERDOSAGE for toxicity information.
INDICATIONS AND USAGE
Acetaminophen and codeine phosphate tablets are indicated for the relief of mild to moderately severe pain.

Codeine-containing products are contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.
This product should not be administered to patients who have previously exhibited hypersensitivity to codeine or acetaminophen.

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 or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.
Codeine is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.
Hepatotoxicity
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The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.
Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4000 milligrams of acetaminophen per day, even if they feel well.
Serious Skin Reactions
Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. 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.
Death Related to Ultra-Rapid Metabolis m of Codeine to Morphine
Respiratory depression and death have occurred in children who received codeine in the post-operative

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 PRECAUTIONS, Nurs ing Mothers].

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). 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. 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 have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) [see OVERDOSAGE].

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 postoperative
pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see CONTRAINDICATIONS].

When prescribing codeine-containing products, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose [see OVERDOSAGE].

Hypers ens itivity/Anaphylaxis

There have been postmarketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue acetaminophen and codeine phosphate tablets, USP immediately and seek medical care if they experience these symptoms. Do not prescribe acetaminophen and codeine phosphate tablets, USP for patients with acetaminophen allergy.

Alcohol Information

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of acetaminophen most often exceed recommended doses and often involve substantial overdose. Professionals should alert their patients who regularly consume large amounts of alcohol not to exceed recommended doses of acetaminophen.

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The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory 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, agranulocytosis.

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

DRUG ABUSE AND DEPENDENCE

Controlled Subs tance

Acetaminophen and codeine phosphate tablets are classified as a Schedule III controlled substance.

Abus e and Dependence

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Following an acute overdosage, toxicity may result from codeine or acetaminophen.

Signs and Symptoms

Toxicity from codeine poisoning includes the opioid triad of: pinpoint pupils, depression of respiration,
and loss of consciousness. Convulsions may occur.

In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and coagulation defects may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment

A single or multiple drug overdose with acetaminophen and codeine is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression due to overdosage or unusual sensitivity to codeine, parenteral naloxone is a specific and effective antagonist.

Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

Dosage should be adjusted according to severity of pain and response of the patient.

The usual adult dosage is:

Single Doses (range)	Maximum 24 Hour Dose
Codeine Phosphate 15 mg to 60 mg	360 mg
Acetaminophen 300 mg to 1000 mg	4000 mg

The usual dose of codeine phosphate in children is 0.5 mg/kg.

Doses may be repeated up to every 4 hours.

The prescriber must determine the number of tablets per dose, and the maximum number of tablets per 24 hours based upon the above dosage guidance. This information should be conveyed in the prescription.

It should be kept in mind, however, 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.

HOW SUPPLIED

Acetaminophen and codeine phosphate tablets USP (white, round, unscored):

Acetaminophen and codeine phosphate tablets USP (white, round, unscored):

List No. 0050, acetaminophen 300 mg and codeine phosphate 15 mg, debossed “2” on one side and “TV”-“50” on the other side of tablet is available in bottles of 100 (NDC 0093-0050-01) tablets.

List No. 0150, acetaminophen 300 mg and codeine phosphate 30 mg, debossed “3” on one side and “TV”-“150” on the other side of tablet is available in bottles of 100 (NDC 0093-0150-01) and 1000 (NDC 0093-0150-10) tablets.

List No. 0350, acetaminophen 300 mg and codeine phosphate 60 mg, debossed “4” on one side and “93”-“350” on the other side of tablet is available in bottles of 100 (NDC 0093-0350-01), 500 (NDC 0093-0350-05), and 1000 (NDC 0093-0350-10) tablets.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture.

PROTECT FROM LIGHT

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Distributed By:

TEVA PHARMACEUTICALS USA, INC.

North Wales, PA 19454

Rev. AI 8/2015

NDC: 61502-903-30

CODEINE PHOSPHATE &
ACETAMINOPHEN

Rx Only

30/300MG
30 Tablets

C III

Lot: Sample Exp: 05/18

Usual adult dosage: See package insert
Store at controlled room temperature: 20-25 C (68-77 F)
Mfg. By: Teva Pharmaceuticals USA
Sellersville, PA 18960 0093-0150-10

Repackaged By: EPM Packaging, Inc. Lexington, NE 68850 SIN: 872521

3 61502 90330 6

ACETAMINOPHEN AND CODEINE PHOSPHATE

acetaminophen and codeine phosphate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61502-903(NDC:0093-0150)
Route of Administration	ORAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	300 mg
CODEINE PHOSPHATE (UNII: GSL05Y1MN6) (CODEINE ANHYDROUS - UNII:UX6OWY2V7J)	CODEINE PHOSPHATE	30 mg

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	3;TV;150
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61502-903-97	500 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2016	
2	NDC:61502-903-96	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2016	
3	NDC:61502-903-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2016	
4	NDC:61502-903-20	20 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2016	
5	NDC:61502-903-15	15 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2016	
6	NDC:61502-903-10	10 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2016	
7	NDC:61502-903-06	6 in 1 BOTTLE; Type 0: Not a Combination Product	01/27/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA088627	01/27/2016	

Labeler - EPM Packaging Inc (079124340)

Registrant - EPM Packaging Inc (079124340)

Establishment

Name	Address	ID/FEI	Business Operations
EPM Packaging Inc		079124340	repack(61502-903)