HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BUTALBITAL, ACETAMINOPHEN, CAFFEINE, AND CODEINE PHOSPHATE CAPSULES safely and effectively. See full prescribing information for BUTALBITAL, ACETAMINOPHEN, CAFFEINE, AND CODEINE PHOSPHATE CAPSULES.

BUTALBITAL, ACETAMINOPHEN, CAFFEINE, and CODEINE PHOSPHATE capsules for oral use. CIII

Initial U.S. Approval: 1992

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE- THREATENING RESPIRATORY DEPRESSION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME, DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and HEPATOTOXICITY

See full prescribing information for complete boxed warning.

- **Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules expose users to the risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Concomitant use of opioids or a barbiturate with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.3, 7)**
- **Accidental ingestion of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, especially by children, can result in fatal overdose. Keep out of reach of children. (5.2)**
- **Prolonged use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life- threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **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. (5.5)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules requires careful consideration of the effects on codeine, and the active metabolite, morphine. (5.6, 7)**
- **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 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. (5.7)**

RECENT MAJOR CHANGES

Boxed Warning	12/2016
Indications and Usage (1)	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

INDICATIONS AND USAGE

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsule is a combination product of butalbital, a barbiturate; acetaminophen; caffeine, a methylxanthine; and codeine phosphate, an opioid agonist; and is indicated for the management of the symptom complex of tension (or muscle contraction) headache, when other non-opioid analgesic and alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for use in patients for whom alternative treatment options (e.g., non-opioid, non-barbiturate analgesics)
- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with one or two capsules every 4 hours as needed for pain. Total daily dosage should not exceed 6 capsules. (2.2)
- Do not stop Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules abruptly in a physically dependent patient. (2.3)

DOSAGE FORMS AND STRENGTHS

- Capsules: 50 mg butalbital, 325 mg acetaminophen, 40 mg caffeine, and 30 mg codeine phosphate.

CONTRAINDICATIONS

- Significant respiratory depression. (4)
- Post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Intolerance or hypersensitivity to acetaminophen, caffeine, butalbital or codeine, or components of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. (4)
- Porphyria. (4)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients with circulatory shock. (5.11)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients with impaired consciousness or coma. (5.12)

ADVERSE REACTIONS

Frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules because they may reduce analgesic effect of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: 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 the baby. (8.2)
- Geriatric: Respiratory depression has occurred after large initial doses were administered. Increase dosage slowly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Issued: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and HEPATOTOXICITY

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Dosage and Administration Instructions
2.2 Dosing Information
2.3 Discontinuation of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Addiction, Abuse, and Misuse
5.2 Life-Threatening Respiratory Depression
5.3 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
5.4 Neonatal Opioid Withdrawal Syndrome
5.5 Death Related to Ultra-Rapid Metabolism of Codeine to Morphine
5.6 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes
5.7 Hepatotoxicity
5.8 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
5.9 Interaction with Monoamine Oxidase Inhibitors
5.10 Adrenal Insufficiency
5.11 Severe Hypotension
5.12 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
5.13 Risks of Use in Patients with Gastrointestinal Conditions
5.14 Increased Risk of Seizures in Patients with Seizure Disorders
5.15 Withdrawal
5.16 Risks of Driving and Operating Machinery
5.17 Serious Skin Reactions
5.18 Hypersensitivity/Anaphylaxis
5.19 Drug/Laboratory Test Interactions
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and HEPATOTOXICITY

Addiction, Abuse, and Misuse

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Monitor for respiratory depression, especially during initiation of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules or following a dose increase *[see Warnings and Precautions (5.2)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids or a barbiturate with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Accidental Ingestion

Accidental ingestion of even one dose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, especially by children, can result in a fatal overdose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)]*.

Death Related To Ultra-Rapid Metabolism 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 *[see Warnings and Precautions (5.5)]*.

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules requires careful consideration of the effects on codeine, and the active metabolite, morphine *[see Warnings and Precautions (5.6)]*.

Hepatotoxicity

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules contain acetaminophen. 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 4,000 milligrams per day, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.7)]*.

1 INDICATIONS AND USAGE

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are indicated for the management of the symptom complex of tension (or muscle contraction) headache when non-opioid analgesic and alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids and butalbital, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for use in patients for whom alternative treatment options [e.g., non-opioid, non-barbiturate analgesics]:
- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5.7)]*.

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

Evidence supporting the efficacy and safety of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in the treatment of multiple recurrent headaches is unavailable.

2.2 Dosing Information

One or two capsules every 4 hours as needed for pain. Total daily dosage should not exceed 6 capsules.

2.3 Discontinuation of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules

While not indicated for around-the-clock therapy, when a patient who has been taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules regularly and may be physically dependent no longer requires therapy with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules abruptly in a physically dependent patient *[see Warnings and Precautions (5.15), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules: Butalbital 50 mg, Acetaminophen 325 mg, Caffeine 40 mg, Codeine Phosphate 30 mg.
Light blue opaque cap with a grey, opaque body. Cap is imprinted in black with "V". Body is imprinted with "3109" in black.

4 CONTRAINDICATIONS

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated in patients with:
- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.5)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.8)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.9), Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)]*
- Known intolerance or hypersensitivity to acetaminophen, caffeine, butalbital, or codeine or to the components of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules
- Porphyria

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules contain codeine. Codeine in combination with butalbital, acetaminophen, and caffeine is a Schedule III controlled substance. As Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules contain butalbital and codeine, they expose users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for addiction, abuse, or misuse prior to prescribing Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, and monitor all patients receiving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, but use in such patients necessitates intensive counseling about the risks and proper use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids and barbiturates are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*.

Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules.

To reduce the risk of respiratory depression, proper dosing and titration of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are essential *[see Dosage and Administration (2.2)]*. Overestimating the Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of (or exposure to) Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, especially by children, can result in respiratory depression and death due to an overdose of codeine and butalbital.

5.3 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and that appropriate treatment will be available *[see Use in Specific Populations (8.1, 8.2), Patient Counseling Information (17)]*.

5.5 Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

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.

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).

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.

5.6 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with codeine are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules requires careful consideration of the effects on codeine and the active metabolite, morphine

- Cytochrome P450 3A4 Interaction

The concomitant use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with all cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome P450 2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

The concomitant use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Patients receiving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and any CYP3A4 inhibitor or inducer for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are used in conjunction with inhibitors and inducers of CYP3A4.

If concomitant use of a CYP3A4 inhibitor is necessary or if a CYP3A4 inducer is discontinued, consider dosage reduction of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.

If concomitant use of a CYP3A4 inducer is necessary or if a CYP3A4 inhibitor is discontinued, consider increasing the Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal *[see Drug Interactions (7)]*.

- Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in codeine plasma concentrations and a decrease in active metabolite morphine plasma concentration which could result in an analgesic efficacy reduction or symptoms of opioid withdrawal.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in codeine plasma concentration and an increase in active metabolite morphine plasma concentration which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression.

Follow patients receiving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and any CYP2D6 inhibitor for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are used in conjunction with inhibitors of CYP2D6.

If concomitant use with a CYP2D6 inhibitor is necessary, follow the patient for signs of reduced efficacy or opioid withdrawal and consider increasing the Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage. After stopping use of a CYP2D6 inhibitor, consider reducing the Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage and follow the patient for signs and symptoms of respiratory depression or sedation *[see Drug Interactions (7)]*.

5.7 Hepatotoxicity

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules contain acetaminophen. 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.

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.

5.8 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules *[see Warnings and Precautions (5.2)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and when Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, codeine's active metabolite, including respiratory depression, coma, and confusion. Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

5.10 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.11 Severe Hypotension

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. In patients with circulatory shock, Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients with circulatory shock.

5.12 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients with impaired consciousness or coma.

5.13 Risks of Use in Patients with Gastrointestinal Conditions

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The codeine in Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.14 Increased Risk of Seizures in Patients with Seizure Disorders

The codeine in Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures occurring in other clinical settings associated with seizures.

Monitor patients with a history of seizure disorders for worsened seizure control during Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules therapy.

5.15 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, in a physically-dependent patient, gradually taper the dosage *[see Dosage and Administration (2.3)]*. Do not abruptly discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in these patients. Abrupt discontinuation of butalbital can cause seizures *[see Drug Abuse and Dependence (9.3)]*.

5.16 Risks of Driving and Operating Machinery

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Butalbital, Acetaminophen,

The possible side effects of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you:

- have trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- are a nursing mother taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, and your breastfeeding baby has increased sleepiness, confusion, difficulty breathing, shallow breathing, limpness, or difficulty breastfeeding.

These are not all the possible side effects of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA-1088.

For more information go to dailymed.nlm.nih.gov, www.parpharm.com or call 1-800-828-9393.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

I11/17 OS2553H-01-1-01

This Medication Guide has been approved by the U.S. Food and Drug Administration.

The possible side effects of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you:

- have trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- are a nursing mother taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, and your breastfeeding baby has increased sleepiness, confusion, difficulty breathing, shallow breathing, limpness, or difficulty breastfeeding.

These are not all the possible side effects of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA-1088.

For more information go to dailymed.nlm.nih.gov, www.parpharm.com or call 1-800-828-9393.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

I11/17 OS2553H-01-1-01

This Medication Guide has been approved by the U.S. Food and Drug Administration.

The possible side effects of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you:

- have trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- are a nursing mother taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, and your breastfeeding baby has increased sleepiness, confusion, difficulty breathing, shallow breathing, limpness, or difficulty breastfeeding.

These are not all the possible side effects of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA-1088.

For more information go to dailymed.nlm.nih.gov, www.parpharm.com or call 1-800-828-9393.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

I11/17 OS2553H-01-1-01

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Codeine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Animal reproduction studies have not been conducted with the combination of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules or with butalbital alone. In animal reproduction studies, codeine administration during organogenesis has been shown to produce delayed ossification in the offspring of mice at 2.8 times maximum recommended human dose (MRHD) of 180 mg/day, embryolethal and fetotoxic effects in the offspring of rats and hamsters at approximately 4 to 6 times the MRHD, and cranial malformations/cranioschisis in the offspring of hamsters between 2 and 8 times the MRHD. Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen.

Treatment of pregnant rats with doses of acetaminophen approximately 2 times the maximum human daily dose (MHDD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately 2 times the MHDD. In mice treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproduction were seen in a continuous breeding study. A reduction in number of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation [*see Data*].

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery

Use of codeine during labor may lead to respiratory depression in the neonate.

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

Published data from a large population-based prospective cohort study and a population-based, case-control study do not clearly report an association with oral acetaminophen and major birth defects, miscarriage, or adverse maternal or fetal outcomes when acetaminophen is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations including recall bias.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Animal Data

Animal reproduction studies have not been conducted with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules or with butalbital alone.

The following data are based on findings from studies performed with either codeine or acetaminophen alone.

Codeine

In a study in which pregnant hamsters were administered 150 mg/kg twice daily of codeine (oral; approximately 14 times the maximum recommended daily dose of 180 mg/day for adults on a mg/m^2 basis) during organogenesis cranial malformations (i.e., meningoencephalocele) in several fetuses were reported, as well as the observation of increases in the percentage of resorptions per litter. Doses of 50 and 150 mg/kg, bid resulted in fetotoxicity as demonstrated by decreased fetal body weight. In an earlier study in hamsters, single oral doses of 73 to 360 mg/kg level on Gestation Day 8 (oral; approximately 4 to 16 times the maximum recommended daily dose of 180 mg/day for adults on a mg/m^2 basis), reportedly produced cranioschisis in all of the fetuses examined.

In studies in rats, doses at the 120 mg/kg level (oral; approximately 6 times the maximum recommended daily dose of 180 mg/day for adults on a mg/m^2 basis) during organogenesis, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation.

In pregnant mice, a single 100 mg/kg dose (subcutaneous; approximately 2.8 times the recommended daily dose of 180 mg/day for adults on a mg/m^2 basis) administered between Gestation Day 7 and 12 reportedly resulted in delayed ossification in the offspring.

No teratogenic effects were observed in rabbits administered up to 30 mg/kg (approximately 4 times the maximum recommended daily dose of 180 mg/day for adults on a mg/m^2 basis) of codeine during organogenesis.

Codeine (30 mg/kg) administered subcutaneously to pregnant rats during pregnancy and for 25 days after delivery increased neonatal mortality at birth. This dose is 1.6 times the maximum recommended human dose of 180 mg/day on a body surface area comparison.

Acetaminophen

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 1.7 the maximum human daily dose (MHDD) of 1950 mg/day based on a body surface area comparison showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 2.4 times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.6 times the MHDD, based on a body surface area comparison. In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.86, 1.7, and 3.4 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

Caffeine

In studies performed in adult animals, caffeine (as caffeine base) administered to pregnant mice as sustained release pellets at 50 mg/kg (less than the maximum recommended daily dose on a mg/m^2 basis), during the period of organogenesis, caused a low incidence of cleft palate and exencephaly in the fetuses.

8.2 Lactation

Risk Summary

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 risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the 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 (5.4)]*.

Acetaminophen is present in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 to 2% of the maternal dose. There is one well-documented report of a rash in a breastfed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use.

Barbiturates and caffeine are also excreted in breast milk in small amounts. Because of potential for serious adverse reactions in nursing infants from Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Clinical Considerations

Infants exposed to Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

Because of potential for serious adverse reactions in nursing infants from Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6). Clinical Pharmacology (12.2). Nonclinical Pharmacology (13.1)]*.

Published literature indicates that acetaminophen affects sperm development in mice with consequent reduction in litter size in a multigeneration study *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Respiratory depression and death have occurred in children with obstructive sleep apnea 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). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

8.5 Geriatric Use

Clinical studies of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Butalbital is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Elderly patients (aged 65 years or older) may have increased sensitivity to Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules slowly in geriatric patients and monitor closely for signs of respiratory depression *[see Warnings and Precautions (5.8)]*.

Components of this product are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of butalbital, codeine, and acetaminophen in this patient population are unknown. Start these patients cautiously with lower doses of codeine sulfate or with longer dosing intervals and titrate slowly while carefully monitoring for side effects.

8.7 Renal Impairment

Codeine pharmacokinetics may be altered in patients with renal failure. Clearance may be decreased and the metabolites may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Start these patients cautiously with lower doses of codeine sulfate or with longer dosing intervals and titrate slowly while carefully monitoring for side effects. In patients with renal disease, monitor effects of therapy with serial renal function tests.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules contain codeine. Codeine in combination with butalbital, acetaminophen, and caffeine is a Schedule III controlled substance.

9.2 Abuse

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules contains codeine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record- keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are for oral use only. Abuse of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules poses a risk of overdose and death. The risk is increased with concurrent use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Butalbital

Barbiturates may be habit-forming. Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than twofold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules should not be abruptly discontinued in a physically-dependent patient *[see Dosage and Administration (2.3)]*. If Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Signs and Symptoms

Symptoms attributable to acute barbiturate poisoning include drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock.

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. Acute caffeine poisoning may cause insomnia, restlessness, tremor, and delirium, tachycardia, and extrasystoles.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to codeine phosphate overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to codeine overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of codeine in Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

A single or multiple drug overdose with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules 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.

11 DESCRIPTION

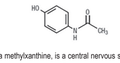
Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are supplied in capsule form for oral administration. Each capsule contains:

Butalbital, USP.....50 mg
Acetaminophen, USP.....325 mg
Caffeine, USP.....40 mg
Codeine phosphate, USP.....30 mg

Butalbital (5-allyl-5-isobutylbarbituric acid), is a short-to intermediate-acting barbiturate. It has the following structural formula:

$C_{11}H_{16}N_2O_3$ MW 224.26

Acetaminophen (4'hydroxyacetanilide), is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW 151.16

Caffeine (1,3,7trimethylxanthine), a methylxanthine, is a central nervous system stimulant. It has the following structural formula:

$C_8H_{10}N_4O_2$ MW 194.19

Codeine phosphate (7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1)(salt) hemihydrate) is an opioid agonist. It has the following structural formula:

$C_{18}H_{24}NO_7P$ anhydrous MW 397.37

Inactive Ingredients: black iron oxide, colloidal silicon dioxide, FD&C Blue #1, gelatin, magnesium stearate, pregelatinized corn starch, sodium lauryl sulfate, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Butalbital, a barbiturate, is a $GABA_A$ receptor agonist and may inhibit excitatory AMPA receptors.

The precise mechanism of the analgesic properties of acetaminophen is not established but is thought to involve central actions.

Caffeine is a methylxanthine and CNS stimulant. The exact mechanism with respect to the indication is not clear; however, the effects of caffeine may be due to antagonism of adenosine receptors.

Codeine is an opioid agonist relatively selective for the mu-opioid receptor, but with a much weaker affinity than morphine. The analgesic properties of codeine have been speculated to come from its conversion to morphine, although the exact mechanism of analgesic action remains unknown.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Butalbital, a barbiturate, is a central nervous system (CNS) depressant that can produce sedation, respiratory depression, and euphoria. The potential impact of butalbital on painful stimuli is not clear and in some individuals barbiturates may increase reaction to painful stimuli.

Codeine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and to electrical stimulation.

Codeine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Acetaminophen has been shown to have analgesic activity in animal and human studies.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Codeine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Butalbital may decrease blood pressure and heart rate when administered at sedative and hypnotic doses.

Codeine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system *in in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent opioids. The minimum effective analgesic concentration of codeine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.2)]*.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing codeine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3)]*.

12.3 Pharmacokinetics

The behavior of the individual components is described below.

Butalbital

Absorption

Butalbital is well absorbed from the gastrointestinal tract.

Distribution

Butalbital is expected to distribute to most tissues in the body. Barbiturates in general may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility. The in vitro plasma protein binding of butalbital is 45% over the concentration range of 0.5 to 20 mcg/mL. This falls within the range of plasma protein binding (20% to 45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood cells.

Elimination

Elimination of butalbital is primarily via the kidney (59% to 88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5-(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with reduction of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% is conjugated. *[See Overdosage (10) for toxicity information]*.

Acetaminophen

Absorption

Acetaminophen is rapidly absorbed from the gastrointestinal tract.

Metabolism

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

Distribution

Acetaminophen is distributed throughout most body tissues. A small fraction (10-25%) of acetaminophen is bound to plasma proteins.

Elimination

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. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. *[See Overdosage (10) for toxicity information]*.

Caffeine

Absorption

Like most xanthines, caffeine is rapidly absorbed.

Distribution

Caffeine is distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Elimination

Caffeine is cleared through metabolism and excretion in the urine.

Metabolism

Caffeine is mainly metabolized by CYP1A2. Other enzymes, including CYP2E1, CYP3A4, CYP2C8 and CYP2C9 may play a minor role in its metabolism. Hepatic biotransformation prior to excretion results in about equal amounts of 1methylxanthine and 1-methyluric acid.

Excretion

Of the 70% of the dose that is recovered in the urine, only 3% is unchanged drug. The plasma half-life is about 3 hours *[See Overdosage (10) for toxicity information]*.

Codeine

Absorption

Codeine is readily absorbed from the gastrointestinal tract. At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

Distribution

Codeine 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.

Elimination

Metabolism

About 70-80% of administered dose of codeine is metabolized by conjugation with glucuronic acid to codeine-6glucuronide (C6G) and via O-demethylation to morph