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: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF BUTALTITAL, ACETAMINOPHEN, CAFFEINE, AND CODEINE PHOSPHATE CAPSULES
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 reassess regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially during initiation and following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are essential. (5.2)**
- **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)**
- **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. (5.3, 7)**
- **If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.4)**
- **Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.5)**
- **Life-threatening respiratory depression and death have occurred in children who received codeine; most cases followed tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism. (5.6). Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4). Avoid the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.**
- **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. (5.7, 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. (5.8)**

RECENT MAJOR CHANGES

Boxed Warning	12/2023
Indications and Usage (1)	12/2023
Dosage and Administration (2.1, 2.3, 2.4)	12/2023
Warnings and Precautions (5.9)	12/2023

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. (1)

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids and butalbital, which can occur at any dosage or duration (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, (1)
- Have not provided adequate analgesia or are not expected to provide adequate analgesia. (1)

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

DOSAGE AND ADMINISTRATION

- Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Consider prescribing naloxone based on the patient's risk factors for overdose. (2.2, 5.1, 5.2, 5.3)

- Initiate treatment with one or two capsules every 4 hours as needed for pain and at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Total daily dosage should not exceed 6 capsules. (2.3, 5)
- Do not abruptly discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5, 5.18)

DOSAGE FORMS AND STRENGTHS

- Capsules: 50 mg butalbital, 325 mg acetaminophen, 40 mg caffeine, and 30 mg codeine phosphate. (3)

CONTRAINDICATIONS

- Children younger than 12 years of age. (4)
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. (4)
- Significant respiratory depression. (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

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.9)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate patients, particularly during initiation and titration. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.12)
- Severe Hypotension: Regularly evaluate patients during dosage initiation and titration. Avoid use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients with circulatory shock. (5.13)
- 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. (5.14)

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 Actavis Pharma, Inc. at 1-800-272-5525 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: Breastfeeding not recommended. (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.

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF BUTALBITAL, ACETAMINOPHEN, CAFFEINE, AND CODEINE PHOSPHATE CAPSULES

Addiction, Abuse, and Misuse

Because the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules exposes 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 and reassess 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, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are essential *[see Warnings and Precautions (5.2)].*

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 codeine *[see Warnings and Precautions (5.2)].*

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

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

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)].*

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the

importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.5)]*.

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being an ultra-rapid metabolizer of codeine due to a CYP2D6 polymorphism *[see Warnings and Precautions (5.6)]*. Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*. Avoid the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine.

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 (5.7)]*.

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 4,000 milligrams per day, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.8)]*.

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, which can occur at any dosage or duration *[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.

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)].* Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.
- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)].*
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5.2)].*

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 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules *[see Warnings and Precautions (5.2).*

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Dosing Information

One or two capsules every 4 hours as needed for pain. Total daily dosage should not exceed 6 capsules. Use the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules.

2.4 Titration and Maintenance of Therapy

Individually titrate Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as to reassess for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1, 5.18)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after a dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.5 Safe Reduction or Discontinuation of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules

Do not abruptly discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules,

there are a variety of factors that should be considered, including the total daily dose of opioid (including Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication-assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.18), 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

Dark blue, opaque cap is imprinted with “WATSON” in light blue. White, opaque body is imprinted with “3220” in red.

4 CONTRAINDICATIONS

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated for:

- All children younger than 12 years of age *[see Warnings and Precautions (5.6)]*
- Post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.6)]*

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are also contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.10)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.11), Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.15)]*
- 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 reassess 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 frequent reevaluation for signs of addiction, abuse, and misuse.

Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Opioids and barbiturates are sought for nonmedical use and are subject to diversion from legitimate prescribed use. 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 careful storage of the drug during the course of treatment and on the proper disposal of unused drug. 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.

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 (2.3)]*. 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 even one dose of 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.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.5)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Inform patients and caregivers about the various ways to obtain naloxone as permitted

by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3), Overdosage (10)]*.

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 and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). 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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.

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).*

5.4 Neonatal Opioid Withdrawal Syndrome

Use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for an extended period of time 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 an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1).*

5.5 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.6 Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years of age appear to be more

susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as post-operative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
- As with adults, when prescribing codeine for adolescents, 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 Use in Specific Populations (8), Overdosage (10)]*.

Nursing Mothers

At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. Breastfeeding is not recommended during treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules *[see Use in Specific Populations (8.2)]*.

CYP2D6 Genetic Variability: Ultra-rapid metabolizer

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 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican).

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 (10)]*. Therefore,

individuals who are ultra-rapid metabolizers should not use Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules.

5.7 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 require 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.

  Evaluate patients receiving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and any CYP3A4 inhibitor or inducer at frequent intervals 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. Evaluate patients at frequent intervals for respiratory depression and sedation.

  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. Evaluate patients at frequent intervals 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.

  Evaluate patients receiving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and any CYP2D6 inhibitor at frequent intervals 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, evaluate patients at frequent intervals 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 evaluate patients at frequent intervals for signs and symptoms of respiratory depression or sedation *[see Drug Interactions (7)]*.

5.8 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 excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

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.

5.9 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect *[see Dependence (9.3)]*.

Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) *[see Dosage and Administration (2.5), Warnings and Precautions (5.18)].*

5.10 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)]*.

Regularly evaluate such patients, 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), Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.11 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.

5.12 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.

5.13 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)]*. Regularly evaluate 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.

5.14 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.

5.15 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. Regularly evaluate patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.16 Hypersensitivity/Anaphylaxis

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the 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 Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules immediately and seek medical care if they experience these symptoms. Do not prescribe Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for patients with acetaminophen allergy.

5.17 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.

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

5.18 Withdrawal

Do not abruptly discontinue Butalbital, Acetaminophen, Caffeine, and Codeine in a patient physically dependent on opioids. Rapid tapering of Butalbital, Acetaminophen, Caffeine, and Codeine in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.5), Drug Abuse and Dependence (9.3)]*.

Additionally, 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 (2.5)]*. Abrupt discontinuation of butalbital can cause seizures *[see Drug Abuse and Dependence (9.3)]*.

5.19 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, Caffeine, and Codeine Phosphate Capsules and know how they will react to the medication.

5.20 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.

5.21 Drug/Laboratory Test Interactions

Codeine: Codeine may increase serum amylase levels.

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

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Interactions with Benzodiazepines and other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children *[see Warnings and Precautions (5.6)]*
- Hepatotoxicity *[see Warnings and Precautions (5.8)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.9)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.12)]*
- Severe Hypotension *[see Warnings and Precautions (5.13)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.15)]*
- Anaphylaxis *[see Warnings and Precautions (5.16)]*
- Seizures *[see Warnings and Precautions (5.17)]*
- Withdrawal *[see Warnings and Precautions (5.18)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.20)]*

The following adverse reactions associated with the use of butalbital, acetaminophen, caffeine, and codeine phosphate were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Frequently Observed

The most frequently reported adverse reactions were drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

Infrequently Observed

All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure. Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.

Autonomic Nervous: dry mouth, hyperhidrosis.

Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular*:* tachycardia.

Musculoskeletal: leg pain, muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.

The following adverse reactions have been voluntarily reported as temporally associated with Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, a related product containing aspirin, butalbital, caffeine, and codeine phosphate.

Central Nervous: abuse, addiction, anxiety, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasms, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse reactions have been reported with the components of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Potential effects of high dosage are listed in the OVERDOSAGE section.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported for butalbital, acetaminophen, and caffeine tablets, USP.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time *[see Clinical Pharmacology (12.2)]*.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.9)]*.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules.

Table 1: Clinically Significant Drug Interactions with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with CYP3A4 inhibitors may result in an increase in codeine plasma concentrations with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules is achieved *[see Warnings and Precautions (5.7)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, it may result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to codeine.
Intervention:	If concomitant use with CYP3A4 inhibitor is necessary, consider dosage reduction of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage until stable drug effects are achieved. Evaluate for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and CYP3A4 inducers can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence *[see Warnings and Precautions (5.7)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the codeine plasma concentration may increase with subsequently greater metabolism by cytochrome CYP2D6, resulting in greater morphine levels *[see Clinical*

	Pharmacology (12.3)], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use of a CYP3A4 inducer is necessary, evaluate the patient at frequent intervals for reduced efficacy and signs of opioid withdrawal and consider increasing the Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage as needed. If a CYP3A4 inducer is discontinued, consider lowering Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules dosage until stable drug effects are achieved. Evaluate patients at frequent intervals for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin
Inhibitors of CYP2D6	
Clinical Impact:	Codeine is metabolized by CYP2D6 to form morphine. The concomitant use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and CYP2D6 inhibitors can increase the plasma concentration of codeine, but can decrease the plasma concentrations of active metabolite morphine, which could result in reduced analgesic efficacy or symptoms of opioid withdrawal, particularly when an inhibitor is added after a stable dose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules is achieved *[see Clinical Pharmacology (12.3)]*. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the codeine plasma concentration will decrease but the active metabolite morphine plasma concentration will increase, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression *[see Clinical Pharmacology (12.3)]*.
Intervention:	If concomitant use with a CYP2D6 inhibitor is necessary, or if a CYP2D6 inhibitor is discontinued after concomitant use, consider dosage adjustment of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and evaluate patients at frequent intervals. If concomitant use with CYP2D6 inhibitors is necessary, evaluate the patient for reduced efficacy or signs and symptoms of opioid withdrawal and consider increasing the dosage of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules as needed. After stopping use of a CYP2D6 inhibitor, consider reducing the dosage of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and evaluate the patient at frequent intervals for signs and symptoms of respiratory depression or sedation.
Examples:	paroxetine, fluoxetine, bupropion, quinidine
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, 5.3)]*.

Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.11)]*.
Intervention:	Do not use Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in patients taking MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses of other opioids (such as oxycodone, hydrocodone, oxymorphone, hydromorphone, or buprenorphine) to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Examples:	phenelzine, tranylcypromine, linezolid
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:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*.
Examples:	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Intervention:	Evaluate 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:	Evaluate 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

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. 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. There are risks to the mother and infant associated with use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for an extended period of time during pregnancy *(see Clinical Considerations).*

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 to 4% and 15 to20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time 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/mg^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 and its active metabolite, morphine, are present in human milk. There are published studies and cases that have reported excessive sedation, respiratory depression, and death in infants exposed to codeine via breast milk. Women who are ultra-rapid metabolizers of codeine achieve higher than expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous in their breastfed infants. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose dependent.

There is no information on the effects of the codeine on milk production. Because of the potential for serious adverse reactions, including excess sedation, respiratory depression, and death in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules *[see Warnings and Precautions (5.6)*].

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

If infants are exposed to Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules through breast milk, they 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.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time 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

The safety and effectiveness of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in pediatric patients have not been established.

Life-threatening respiratory depression and deaths have occurred in children who received codeine *[see Warnings and Precautions (5.6)]*. In most of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and many of the children 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). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of codeine. Because of the risk of life-threatening respiratory depression and death:

- Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated for post-operative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation, such as post-operative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression *[see Warnings and Precautions (5.6)]*.

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 frequently reevaluate the patient for signs of respiratory depression *[see Warnings and Precautions (5.10)]*.

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 regularly evaluate 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 regularly evaluating 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 regularly evaluating for side effects. In patients with renal disease, regularly evaluate 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 high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules abuse include those with a history of prolonged use of any opioid, including products containing codeine, those with a history of drug or alcohol abuse, or those who use Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in combination with other abused drugs.

"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 people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, like other opioids, can be diverted for nonmedical 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 reevaluation 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

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/or other CNS depressants.

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are approved for oral use only.

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 use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), 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 use.

Do not abruptly discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in a patient physically dependent on opioids. Rapid tapering of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules gradually taper the dosage using a patient-specific plan that considers the following: the dose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.5), Warnings and Precautions (5.18)]*.

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 codeine 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, hypoglycemia, 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 re-establishment 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 measures.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.

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:

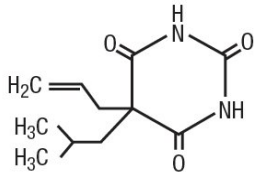
Butalbital, USP…….....50 mg

Acetaminophen, USP……...325 mg

Caffeine, USP…….....40 mg

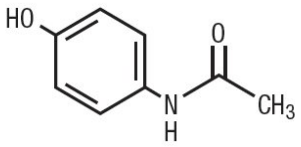
Codeine phosphate, USP….....30 mg

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



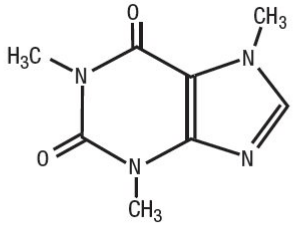
$C_{11}H_{16}N_2O_3$ MW 224.26

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



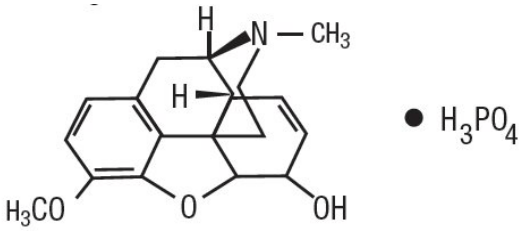
$C_8H_9NO_2$ MW 151.16

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: colloidal silicon dioxide, magnesium stearate, pregelatinized starch. Gelatin capsules contain D&C Red No. 33, FD&C Blue No. 1, gelatin, and titanium dioxide. The capsules are printed with edible inks containing D&C Red No. 7 Calcium Lake, FD&C Blue No. 1 Aluminum Lake, 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.

Use of opioids for an extended period of time 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 opioid agonists. 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, 2.3)]*.

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, 2.3, 2.5)]*.

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 excretion 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 morphine (about 5-10%) and *N*-demethylation to norcodeine (about 10%) respectively. UDP-glucuronosyltransferase (UGT) 2B7 and 2B4 are the major enzymes mediating glucuronidation of codeine to C6G. Cytochrome P450 2D6 is the major enzyme responsible for conversion of codeine to morphine and P450 3A4 is the major enzyme mediating conversion of codeine to norcodeine. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Morphine and M6G are known to have analgesic activity in humans. The analgesic activity of C6G in humans is unknown. Norcodeine and M3G are generally not considered to possess analgesic properties.

Excretion

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 (about 4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

[See Overdosage (10) for toxicity information].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of the combination of butalbital, acetaminophen, caffeine, and codeine or butalbital alone have not been conducted.

Two-year carcinogenicity studies with codeine sulfate have been conducted in F344/N rats and B6C3F1 mice. There was no evidence of carcinogenicity in male and female rats, respectively, at dietary doses up to 70 and 80 mg/kg/day of codeine sulfate (approximately 4 times the maximum recommended daily dose of 180 mg/day for adults on a mg/m^2 basis) for two years. Similarly there was no evidence of carcinogenicity activity in male and female mice at dietary doses up to 400 mg/kg/day of codeine sulfate (approximately 10 times the maximum recommended daily dose of 180 mg/day for adults on a mg/m^2 basis) for two years.

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 1.6 times the maximum human daily dose (MHDD) of 1950 mg/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 1.4 times or mice at up to 2.4 to 2.8 times the MHDD, based on a body surface area comparison.

In a 2-year study in Sprague-Dawley rats, caffeine (as caffeine base) administered in drinking water was not carcinogenic in male rats at doses up to 102 mg/kg or in female rats at doses up to 170 mg/kg (approximately 4 and 7 times, respectively, the maximum human daily dose on a mg/m^2 basis). In an 18-month study in C57BL/6 mice, no evidence of tumorigenicity was seen at dietary doses up to 55 mg/kg (equivalent to the MHDD on a mg/m^2 basis).

Mutagenesis

There are no genetic toxicology data for butalbital.

Codeine sulfate was not mutagenic in the in vitro bacterial reverse mutation assay or clastogenic in the in vitro Chinese hamster ovary cell chromosome aberration assay.

In the published literature, acetaminophen has been reported to be clastogenic when administered at 1500 mg/kg/day to the rat model (7.2-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (3.6-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Caffeine (as caffeine base) increased the sister chromatid exchange (SCE) SCE/cell metaphase (exposure time dependent) in an in vivo mouse metaphase analysis. Caffeine also potentiated the genotoxicity of known mutagens and enhanced the micronuclei formation (5-fold) in folate-deficient mice. However, caffeine did not increase chromosomal aberrations in in vitro Chinese hamster ovary cell (CHO) and human lymphocyte assays and was not mutagenic in an in vitro CHO/hypoxanthine guanine phosphoribosyltransferase (HGPRT) gene mutation assay, except at cytotoxic concentrations. In addition, caffeine was not clastogenic in an in vivo mouse micronucleus assay. Caffeine was negative in the in vitro bacterial reverse mutation assay (Ames test).

Impairment of Fertility

No adequate studies have been conducted in animals to characterize the impact of the combinations of butalbital, acetaminophen, caffeine, and codeine on fertility. There are also no data on butalbital alone or codeine alone.

In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 3.4 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 3.6 times the MHDD (based on a body surface comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 2.4 times the MHDD and greater (based on a body surface comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

Caffeine (as caffeine base) administered to male rats at 50 mg/kg/day subcutaneously (2 times the MHDD on a mg/m^2 basis) for 4 days prior to mating with untreated females, caused decreased male reproductive performance in addition to causing embryotoxicity. In addition, long-term exposure to high oral doses of caffeine (3 g over 7 weeks) was toxic to rat testes as manifested by spermatogenic cell degeneration.

16 HOW SUPPLIED/STORAGE AND HANDLING

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules:
Dark blue, opaque cap is imprinted with “WATSON” in light blue. White, opaque body is imprinted with “3220” in red. Bottles of 100 are supplied with child-resistant closures (NDC 0591-3220-01).

Store below 30°C (86°F); and dispense in a tight container.

Store Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules securely and dispose of properly.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)]*. Inform

patients that leaving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that medicine take-back options are the preferred way to safely dispose of most types of unneeded medicines. If no take back programs or DEA-registered collectors are available, instruct patients to dispose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules by following these four steps:

- Mix Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules (do not crush) with an unpalatable substance such as dirt, cat litter, or used coffee grounds;
- Place the mixture in a container such as a sealed plastic bag;
- Throw the container in the household trash;
- Remove all personal information on the prescription label of the empty bottle

Inform patients that they can visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with others and to take steps to protect Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants (Including Alcohol)

Inform patients and caregivers that potentially fatal additive effects may occur if Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-threatening Respiratory Depression in Children

Advise caregivers that Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are contraindicated in all children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children 12-18 years of age receiving codeine to watch for signs of respiratory depression *[see Warnings and Precautions (5.6)]*.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.9), Adverse Reactions (6)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition called serotonin syndrome resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients not to take Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs

while taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules *[see Drug Interactions (7)*].

Important Administration Instructions

Instruct patients how to properly take Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, including the following:

- To take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed *[see Dosage and Administration (2.1, 2.3)].*
- Do not take more than 4000 milligrams of acetaminophen per day and to call their healthcare provider if they took more than the recommended dose.

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.5)].*

Risks of Driving and Operating Heavy Machinery

Inform patients that Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.19)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.12)]*.

Severe Hypotension

Inform patients that Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.13)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)].*

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise women that breastfeeding is not recommended during treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6)]*.

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Medication Guide

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, C III

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is indicated for the relief of the symptom complex of tension (or muscle contraction) headache, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules:

- **Get emergency help or call 911 right away if you take too much Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules (overdose)**. When you first start taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules. They could die from taking it. Selling or giving away Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules is against the law.
- Store Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
- Get emergency help right away if you take more than 4,000 mg of acetaminophen in 1 day. Taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with other products that contain acetaminophen can lead to serious liver problems and death.

Important Information Guiding Use in Pediatric Patients:

- Do not give Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules to a child younger than 12 years of age.
- Do not give Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
- Avoid giving Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules to children between 12 to 18 years of age who have risk factors for breathing problems such as obstructive sleep apnea, obesity, or underlying lung problems.

Do not take Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.
- Have been told by your healthcare provider that you are a “rapid metabolizer” of certain medicines

Tell your healthcare provider if you are:

- **Noticing your pain getting worse.** If your pain gets worse after you take Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, do not take more of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules.
- **pregnant or planning to become pregnant.** Use of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules; may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules with certain other medicines can cause serious side effects that could lead to death.

When taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules:

- Do not change your dose. Take Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- For acute (short-term) pain, you may only need to take Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules for a few days. You may have some Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules.
- Take your prescribed dose of 1 or 2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules regularly, do not stop taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules without talking to your healthcare provider.

- After you stop taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules, dispose the unused Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules in accordance with the local state guidelines and/or regulations.
- Dispose of expired, unwanted, or unused Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules by taking your drug to an authorized DEA-registered collector or drug take-back program. If one is not available, you can dispose of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules by mixing the product with dirt, cat litter, or coffee grounds; placing the mixture in a sealed plastic bag, and throwing the bag in your trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules DO NOT:

- Drive or operate heavy machinery, until you know how Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules affect you. Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules may cause you to overdose and die.

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 or call 911 right away 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**

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This Medication Guide has been approved by the U.S. Food and Drug Administration. **Revised: 12/2023**