

ASCOMP WITH CODEINE- butalbital, aspirin, caffeine, and codeine phosphate capsule
LGM PHARMA SOLUTIONS, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP safely and effectively. See full prescribing information for Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP for oral use, CIII initial U.S. Approval: 1990

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

See full prescribing information for complete boxed warning.

- Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP exposes users to the risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)
- Accidental ingestion of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, especially by children, can result in fatal overdose. (5.2)
- Concomitant use of opioids or a barbiturate with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.3, 5.9, 7)
- Prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- 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. (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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP requires careful consideration of the effects on codeine, and the active metabolite, morphine. (5.7, 5.9, 7)

RECENT MAJOR CHANGES

Warnings and Precautions (5.21) 07/2024

INDICATIONS AND USAGE

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is a combination of butalbital, a barbiturate, aspirin, a nonsteroidal anti-inflammatory drug, 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 analgesics and alternative treatments are inadequate.

Limitations of Use:

Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration (5.1) reserve Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Initiate treatment with one or two capsules every 4 hours as needed for pain, and at the lowest dose necessary to achieve adequate analgesic. Titrate the dose based upon the individual patient's response to their initial dose of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. Total daily dose should not exceed 6 capsules. (2, 5)

DOSAGE FORMS AND STRENGTHS

- Capsules: 50 mg butalbital, 325 mg aspirin, 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 (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)
- Hypersensitivity to aspirin, caffeine, butalbital, or codeine (4)
- Hemophilia (4)
- Reye's Syndrome (4)
- Known allergy to NSAIDs (4)
- Syndrome of asthma, rhinitis, and nasal polyps (4)

WARNINGS AND PRECAUTIONS

- **Opioid-Induced Hypoalgesia and Allodynia:** Opioid-Induced Hypoalgesia (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. (5.8)
- **Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients:** Regularly evaluate closely, particularly during initiation and titration. (5.9)
- **Adrenal Insufficiency:** If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid. (5.11)
- **Severe Hypotension:** Regularly evaluate during dose initiation and titration. Avoid use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP in patients with circulatory shock. (5.12)
- **Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness:** Regularly evaluate for sedation and respiratory depression. Avoid use of Butalbital, Aspirin, Caffeine, and Codeine Capsules, USP in patients with impaired consciousness or coma. (5.13)
- **Fetal Toxicity:** Limit use of NSAIDs, including Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.17, 8.1).
- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** Discontinue and evaluate clinically (5.22).

ADVERSE REACTIONS

- Most common adverse reactions (incidence > 1%) are nausea and/or abdominal pain, drowsiness, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact LGM Pharma Solutions, LLC at 1-877-

288-1495 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP if serotonin syndrome is suspected. (7)
- **Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics:** Avoid use with Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP because they may reduce analgesic effect of Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2024

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FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse

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

Accidental Ingestion

Accidental ingestion of even one dose of Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP, especially by children, can result in a fatal overdose of aspirin, butalbital, caffeine, and codeine phosphate [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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 important 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP requires careful consideration of the effects on codeine, and the active metabolite, morphine [see *Warnings and Precautions (5.7,5.9), Drug Interactions (7)*].

1 INDICATIONS AND USAGE

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is 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, which can occur at any dosage or duration [see *Warnings and Precautions (5.1)*], reserve Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP for use in patients for whom alternative treatment options [e.g., non-opioid analgesic or opioid combination products]:

- 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 a 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. Consider this risk when selecting an initial dose and when making dose adjustments [see *Warnings and Precautions (5)*].

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of the opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP [see *Warnings and Precautions (5.2), Patient Counseling Information (17)*].

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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.

2.4 Safe Reduction or Discontinuation of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP

Do not abruptly discontinue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, there are a variety of factors that should be considered, including the total daily dose of opioid (including Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP) 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 analgesics [see *Warnings and Precautions (5.16), Drug Abuse and Dependence (9.3)*].

3 DOSAGE FORMS AND STRENGTHS

Capsules: Butalbital, 50 mg, Aspirin, 325 mg, Caffeine, 40 mg, Codeine Phosphate, 30 mg
Plain blue opaque cap with a yellow opaque body imprinted with "B 074" in black ink.

4 CONTRAINDICATIONS

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules,

USP is contraindicated for:

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

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules,

USP is also contraindicated in patients with:

- Significant respiratory depression [see *Warnings and Precautions (5.9)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions (5.9)*]
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [see *Warnings and Precautions (5.10), Drug Interactions (7)*].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.14)*]
- Hypersensitivity or intolerance to aspirin, caffeine, butalbital, or codeine.
- Hemophilia [see *Warnings and Precautions (5.19)*]
- Reye's Syndrome [see *Warnings and Precautions (5.20)*]
- Known allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) [see *Warnings and Precautions (5.23)*]
- Syndrome of asthma, rhinitis, and nasal polyps [see *Warnings and Precautions (5.23)*]

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP contains codeine. Codeine in combination with butalbital, aspirin, and caffeine is a Schedule III controlled substance. As Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP contains butalbital and codeine, it exposes 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. 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, Aspirin, Caffeine, and Codeine Phosphate, USP, and reassess all patients receiving Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, but use in such patients necessitates intensive counseling about the risks and proper use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. 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 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 (CO₂) 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP are essential [see *Dosage and Administration (2.1)*]. Overestimating the Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, 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 [see *Patient Counseling Information (17)*].

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 (2.4)*].

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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. 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 [see *Patient Counseling Information (17)*].

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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP with benzodiazepines 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)*].

Advise both patients and caregivers about the risks of respiratory depression and sedation when Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is 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)* and *Patient Counseling Information (17)*].

5.4 Neonatal Opioid Withdrawal Syndrome

Use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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)*, *Patient Counseling Information (17)*].

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 Healthcare Providers Involved in the Management of 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 patient 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 postmarketing reports, children younger than 12 years old 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 may be particularly sensitive to its respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is contraindicated for all children younger than 12 years of age [see *Contraindications (4)*].
- Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 postoperative 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 Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 (8.4)*, *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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP [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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.

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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP requires careful consideration of the effects on codeine and the active metabolite, morphine.

Cytochrome P450 3A4 Interaction

The concomitant use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and any CYP3A4 inhibitor or inducer at frequent intervals for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when Butalbital, Aspirin, Caffeine,

and Codeine Phosphate Capsules, USP is 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and any CYP2D6 inhibitor at frequent intervals for signs and symptoms that may reflect opioid toxicity and opioid withdrawal when Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP dosage. After stopping use of a CYP2D6 inhibitor, consider reducing the Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP dosage and evaluate patients at frequent intervals for signs and symptoms of respiratory depression or sedation. [see *Drug Interactions (7)*].

5.8 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.

Causes 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 (2.4)*; *Warnings and Precautions (5.16)*].

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

The use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP-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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP [see *Warnings and Precautions (5.9)*].

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 (5.9)*].

Regularly evaluate patients, particularly when initiating and titrating Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and when Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5)*, *Drug Interactions (7)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

5.11 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.

5.12 Severe Hypotension

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. In patients with circulatory shock, Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP in patients with circulatory shock.

5.13 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 CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Butalbital,

Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.

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

5.14

Risks of Use in Patients with Gastrointestinal Conditions Including Peptic Ulcer Disease

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is contraindicated in patients

with known or suspected gastrointestinal obstruction, including paralytic ileus.

The codeine in Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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.

Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

The aspirin in Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP can cause GI side effects including stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders

The codeine in Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP therapy.

5.16 Withdrawal

Do not abruptly discontinue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP in a patient physically dependent on opioids. Rapid tapering of butalbital, aspirin, caffeine, and codeine phosphate capsules in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see *Dosage and Administration (2.4)*, *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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms. [see *Drug Interactions (7)*].

When discontinuing Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP in a physically-dependent patient, gradually taper the dosage [see *Dosage and Administration (2.4)*]. Abrupt discontinuation of butalbital can cause seizures [see *Drug Abuse and Dependence (9.3)*].

5.17 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, in pregnant women about 30 weeks gestation and later. NSAIDs, including Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP treatment extends beyond 48 hours. Discontinue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP if oligohydramnios occurs and follow up according to clinical practice [see *Use in Specific Populations (8.1)*].

5.18 Risks of Driving and Operating Machinery

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and know how they will react to the medication.

5.19 Coagulation Abnormalities and Bleeding Risks

Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (i.e. hemophilia) or acquired (i.e. liver disease or vitamin K deficiency) bleeding disorders. Aspirin is contraindicated in patients with hemophilia.

Aspirin administered pre-operatively may prolong the bleeding time.

Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

5.20 Reye's Syndrome

Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

5.21 Serious Skin Reactions

NSAIDs, including aspirin, a component of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP at the first appearance of skin rash or any other sign of hypersensitivity. Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is contraindicated in patients with previous serious skin reactions to NSAIDs [see *Contraindications (4)*].

5.22 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. Some of these events have been fatal or life threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and evaluate the patient immediately.

5.23 Allergy

Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products (NSAIDs) and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

5.24 Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxy-indoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

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)]
- Risks from Concomitant Use with Benzodiazepines or 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)]
- Opioid-Induced Hyperalgesia and Allodynia [see *Warnings and Precautions* (5.8)]
- Adrenal Insufficiency [see *Warnings and Precautions* (5.11)]
- Severe Hypotension [see *Warnings and Precautions* (5.12)]
- Risk of Use in Patients with Gastrointestinal Conditions Including Peptic Ulcer Disease [see *Warnings and Precautions* (5.14)]
- Increase Risk of Seizures in Patients with Seizure Disorders [see *Warnings and Precautions* (5.15)]
- Withdrawal [see *Warnings and Precautions* (5.16)]
- Coagulation Abnormalities and Bleeding Risks [see *Warnings and Precautions* (5.19)]
- Reye's Syndrome [see *Warnings and Precautions* (5.20)]
- Serious Skin Reactions [see *Warnings and Precautions* (5.21)]
- Allergy [see *Warnings and Precautions* (5.23)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Incidence in Controlled Clinical Trials:

The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules treated patients in controlled clinical trials comparing Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules Treated Patients During Placebo Controlled Clinical Trials

Body System/Adverse Event	Incidence Rate of Adverse Events	
	Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules (N=382)	Placebo (N=377)

Central Nervous

Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%

Gastrointestinal

Nausea/Abdominal Pain	3.7%	0.8%
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Other Adverse Events Reported During Controlled Clinical Trials

The listing that follows represents the proportion of the 382 patients exposed to Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table,

are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules, the adverse events were not necessarily caused by Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. 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, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

The following adverse drug reactions have been reported with the components of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.

Potential effects of high dosage are listed in the [see *Overdosage (10)*] section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

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

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules. Because these reactions are 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.

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

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

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

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

Skin: erythema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), hives, rash, toxic epidermal necrolysis, and fixed drug eruption (FDE).

Urinary: kidney impairment, urinary difficulty.

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

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.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration [see *Warnings and Precautions (5.8)*].

Hyperglycemia: 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.

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

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is achieved. 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 <i>Clinical Pharmacology (12.3)</i>], 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and CYP3A4 inducers can result in lower codeine levels, greater norcodeine levels, and less metabolism via 2D6 with resultant lower morphine levels [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence [see <i>Warnings and Precautions (5.16)</i>]. 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 <i>Clinical Pharmacology (12.3)</i>], 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 patients at frequent intervals for reduced efficacy and signs of opioid withdrawal and consider increasing the Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP dosage as needed. If a CYP3A4 inducer is discontinued, consider Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP dosage reduction, and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
Examples:	Rifampin, carbamazepine, phenytoin
Inhibitors of CYP2D6	
Clinical Impact:	Codeine in Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is metabolized by CYP2D6 to form morphine. The concomitant use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is achieved [see <i>Clinical Pharmacology (12.3)</i>]. 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 <i>Clinical Pharmacology (12.3)</i>].
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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and evaluate patients at frequent intervals. If concomitant use with CYP2D6 inhibitors is necessary, evaluate patients for reduced efficacy or signs and symptoms of opioid withdrawal and consider increasing the Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP as needed. After stopping use of a CYP2D6 inhibitor, consider reducing the Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and evaluate patients 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, increases the risk of 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.
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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP immediately if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that effect 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 <i>Warnings and Precautions (5.10)</i>].

Intervention:	Do not use Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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:	Evaluate patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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.
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. The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.
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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is used concomitantly with anticholinergic drugs.
Anticoagulants	
Clinical Impact:	Aspirin may enhance the effects of anticoagulants. Concurrent use may increase the risk of bleeding. Aspirin can also displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time.
Intervention:	Evaluate patients for signs of bleeding.
Examples:	Warfarin, heparin, enoxaparin, clopidogrel, prasugrel, rivaroxaban, apixaban
Uricosuric Agents	
Clinical Impact:	Aspirin inhibits the uricosuric effects of uricosuric agents.
Intervention:	Avoid concomitant use.
Examples:	Probenecid
Carbonic Anhydrase Inhibitors	
Clinical Impact:	Concurrent use with aspirin can lead to high serum concentrations of the carbonic anhydrase inhibitor and cause toxicity due to competition at the renal tubule for secretion.
Intervention:	Consider reducing the dose of the carbonic anhydrase inhibitor. Evaluate the patients for any adverse effects from the carbonic anhydrase inhibitor.
Examples:	Acetazolamide, methazolamide
Methotrexate	
Clinical Impact:	Aspirin may enhance the toxicity of methotrexate by displacing it from its plasma protein binding sites and/or reducing its renal clearance.
Intervention:	Use caution if using concomitantly, especially in elderly patients or patients with renal impairment. Evaluate patients for methotrexate toxicity.
Nephrotoxic Agents	
Clinical Impact:	Concomitant use with aspirin may lead to additive nephrotoxicity due to the inhibition of renal prostaglandins by aspirin. Also, the plasma concentration of aspirin is increased by conditions that reduce the glomerular filtration rate or tubular secretion.
Intervention:	Use Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP with caution if used concomitantly with nephrotoxic agents. Evaluate the renal function of patients.
Examples:	Aminoglycosides, amphotericin B, systemic bacitracin, cisplatin, cyclosporine, foscarnet, or parenteral vancomycin
Angiotensin Converting Enzyme (ACE) Inhibitors	
Clinical Impact:	The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.
Intervention:	Use caution if using concomitantly. Evaluate the blood pressure and renal function of patients.
Examples:	Ramipril, captopril
Beta Blockers	
Clinical Impact:	The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.
Intervention:	Use caution if using concomitantly. Evaluate the blood pressure and renal function of patients.
Examples:	Metoprolol, propranolol
Hypoglycemic Agents	
Clinical Impact:	Aspirin may increase the serum glucose-lowering action of insulin and sulfonylureas leading to hypoglycemia.
Intervention:	Patients should be advised to consult a physician if any signs or symptoms of hypoglycemia occur.
Examples:	Insulin, glimepiride, glipizide
Anticonvulsants	
Clinical Impact:	Aspirin can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.
Intervention:	Use caution if using concomitantly.
Examples:	Phenytoin, valproic acid
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	
Clinical Impact:	Concurrent use with aspirin may increase the risk of bleeding or lead to decreased renal function. Aspirin may enhance serious side effects and toxicity of ketorolac by displacing it from its plasma protein binding sites and/or reducing its renal clearance.
Intervention:	Avoid concomitant use.
Examples:	Ketorolac, ibuprofen, naproxen, diclofenac
Corticosteroids	
Clinical Impact:	In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in sialcylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.
Intervention:	Avoid concomitant use.

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)]. Use of NSAIDs, including aspirin, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP use between about 20 and 30 weeks of gestation, and avoid Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP use at about 30 weeks of gestation and later in pregnancy [see *Clinical Considerations, Data*].

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including aspirin, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Animal reproduction studies have not been conducted with the combination of butalbital, aspirin, 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 [see *Data*]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as aspirin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) 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% to 20%, 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)].

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, can cause premature closure of the fetal ductus arteriosus (see *Data*).

Oligohydramnios/Neonatal Renal Impairment:

If NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP and follow up according to clinical practice [see *Data*].

Labor or Delivery

There are no studies on the effects of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP during labor or delivery. In animal studies, NSAIDs, including aspirin, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Opioids such as codeine 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate.

Opioid analgesics, including Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, 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.

Aspirin should be avoided one week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

Animal reproduction studies have not been conducted with the combination of butalbital, aspirin, caffeine, and codeine phosphate capsules or with butalbital 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/m² 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/m² 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/m² 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/mg² 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/m² 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.

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/m² 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP [see *Warnings and Precautions*, (5.7)].

The aspirin and caffeine in Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP are also excreted in breast milk in small amounts.

Adverse effects on platelet function in the nursing infant exposed to aspirin in breast milk may be a potential risk. Furthermore, nursing women are advised against aspirin use because of the possible development of Reye's Syndrome in their babies.

Barbiturates and caffeine are also excreted in breast milk in small amounts. Because of potential for serious adverse reactions in nursing infants from butalbital, aspirin, 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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* (6.2), *Clinical Pharmacology* (12.2), *Nonclinical Toxicology* (13.1)].

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including aspirin, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including aspirin, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Preparations containing aspirin should be kept out of the reach of children. Reye's Syndrome is a rare condition that affects the brain and liver and is most often observed in children given aspirin during a viral illness. Safety and effectiveness in pediatric patients have not been established.

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

Life-threatening respiratory depression and death 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is contraindicated for all children younger than 12 years of age [see *Contraindications* (4)].
- Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 postoperative 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, Aspirin, Caffeine, and Codeine Phosphate, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression [see *Warnings and Precautions* (5.9)].

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

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, dose selection should start at the low end of the dosing range, and monitor patients for adverse effects [see *Warnings and Precautions* (5)].

8.6 Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment so the pharmacokinetics of aspirin, codeine and butalbital in this patient population are unknown. Start these patients cautiously with lower doses of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP or with longer dosing intervals and titrate slowly while carefully monitoring for side effects. In patients with severe hepatic disease, monitor effects of therapy with serial liver function tests.

8.7 Renal Impairment

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP contains aspirin, which should be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

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 Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP or with longer dosing intervals and titrate slowly while carefully monitoring for side effects. In patients with renal disease, monitor effects of therapy with serial renal function tests.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP contains codeine. Codeine in combination with butalbital, aspirin, and caffeine is a Schedule III controlled substance.

9.2 Abuse

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP contains aspirin, butalbital, caffeine, and codeine phosphate, a substance with a 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 over than activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP with alcohol and 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP abuse include those with a history of prolonged use of any opioid, including products containing aspirin, butalbital, caffeine, and codeine phosphate, those with a history of drug or alcohol abuse, or those who use Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 abuse disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

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

Proper assessment of the patient, proper prescribing practices, periodic 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP

Abuse of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP poses a risk of overdose and death. The risk is increased with concurrent abuse of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP with alcohol and/or other CNS depressants.

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is approved for oral use only.

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

9.3 Dependence

Both tolerance and physical dependence can develop during chronic 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP in a patient physically dependent on opioids. Rapid tapering of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, gradually taper the dosage using a patient-specific plan that considers the following: the dose of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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* (2.4), *Warnings and Precautions* (5.16)].

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

10 OVERDOSAGE

Clinical Presentation

Acute overdose with Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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

Acute Barbiturate Poisoning:

Symptoms include drowsiness, confusion, and coma; respiratory depression; hypotension; hypovolemic shock.

Acute Aspirin Poisoning:

Symptoms include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus, hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions.

Acute Caffeine Poisoning:

Symptoms include insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles.

Codeine:

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, 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)].

Treatment of Overdose

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

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. The value of vasopressor agents such as Norepinephrine or Phenylephrine Hydrochloride in treating hypotension is questionable since they increase vasoconstriction and decrease blood flow. However, if prolonged support of blood pressure is required, Norepinephrine Bitartrate (Levophed®) may be given I.V. with the usual precautions and serial blood pressure monitoring. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

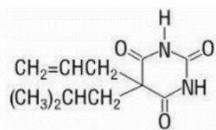
11 DESCRIPTION

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is supplied in capsule form for oral administration.

Each capsule contains the following active ingredients:

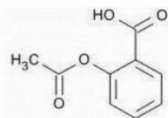
Butalbital, USP.....50mg
Aspirin, USP.....325mg
Caffeine, USP.....40mg
Codeine phosphate, USP.....30mg

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



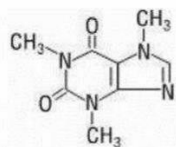
$C_{17}H_{16}N_2O_5$ molecular weight 224.26

Aspirin (benzoic acid, 2-(acetoxy-)) is a nonsteroidal anti-inflammatory drug. It has the following structural formula:



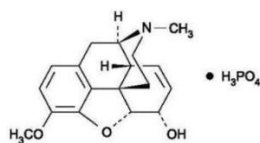
$C_9H_8O_4$ molecular weight 180.16

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



$C_8H_{10}N_4O_2$ molecular weight 194.19

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



$C_{18}H_{22}NO_5 \cdot P$ anhydrous molecular weight 397.37

Inactive Ingredients: Corn Starch, D&C Red No. 28, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, Gelatin, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Stearic Acid, Talc, and Titanium Dioxide. The capsules are printed with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Aspirin is a nonsteroidal anti-inflammatory drug and a non-selective irreversible inhibitor of cyclooxygenases.

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 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.

Aspirin works by inhibiting the body's production of prostaglandins, including prostaglandins involved in inflammation.

Prostaglandins cause pain sensations by stimulating muscle contractions and dilating blood vessels throughout the body. In the CNS, aspirin works on the hypothalamus heat-regulating center to reduce fever, however, other mechanisms may be involved.

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.

Aspirin can produce gastrointestinal injury (lesions, ulcers) through a mechanism that is not yet completely understood, but may involve a reduction in eicosanoid synthesis by the gastric mucosa. Decreased production of prostaglandins may compromise the defenses of the gastric mucosa and the activity of substances involved in tissue repair and ulcer healing.

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, sweating, and/or orthostatic hypotension.

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclooxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor, thromboxane A₂. Nonacetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin 12 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see *Adverse Reactions* (6.2)]. 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* (6.2)].

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, 2.4)].

12.3 Pharmacokinetics

Bioavailability:

The bioavailability of the components of the fixed combination of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is identical to their bioavailability when Butalbital, Aspirin, and Caffeine Capsules and codeine are administered separately in equivalent molar doses. The behavior of the individual components is described below.

Aspirin

Absorption

The systemic availability of aspirin after an oral dose is highly dependent on the dosage form, the presence of food, the gastric emptying time, gastric pH, antacids, buffering agents, and particle size. These factors affect not necessarily the extent of absorption of total salicylates but more the stability of aspirin prior to absorption.

Distribution

During the absorption process and after absorption, aspirin is mainly hydrolyzed to salicylic acid and distributed to all body tissues and fluids, including fetal tissues, breast milk, and the central nervous system (CNS). Highest concentrations are found in plasma, liver, renal cortex, heart, and lung. In plasma, about 50%-80% of the salicylic acid and its metabolites are loosely bound to plasma proteins.

Elimination

Metabolism

The biotransformation of aspirin occurs primarily in the hepatocytes. The major metabolites are salicylic acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and gentisuric acid (1%). The bioavailability of the aspirin component of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is equivalent to that of a solution except for a slower rate of absorption. A peak concentration of 8.8 mcg/mL was obtained at 40 minutes after a 650 mg dose.

Excretion

The clearance of total salicylates is subject to saturable kinetics; however, first-order elimination kinetics are still a good approximation for doses up to 650 mg. The plasma half-life for aspirin is about 12 minutes and for salicylic acid and/or total salicylates is about 3 hours.

The elimination of therapeutic doses is through the kidneys either as salicylic acid or other biotransformation products. The renal clearance is greatly augmented by an alkaline urine as is produced by concurrent administration of sodium bicarbonate or potassium citrate.

Codeine

Absorption

Codeine is readily absorbed from the gastrointestinal tract. The bioavailability of the codeine component of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is equivalent to that of a solution. Peak concentrations of 198 ng/mL were obtained at 1 hour after a 60 mg dose. At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

Distribution

It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen, and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain, however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

Elimination

Metabolism

About 70-80% of administered dose of codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (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 (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

Butalbital

Absorption

Butalbital is well absorbed from the gastrointestinal tract. The bioavailability of the butalbital component of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is equivalent to that of a solution except for a decrease in the rate of absorption. A peak concentration of 2,020 ng/mL is obtained at about 1.5 hours after a 100 mg dose.

Distribution

Butalbital is expected to distribute to most of the 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 included parent drug (about 3.6% of the dose), 5-isobutyl-5- (2,3-dihydroxypropyl) 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% was conjugated.

Caffeine

Absorption

Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk. The bioavailability of the caffeine component for Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is equivalent to that of a solution except for a slightly longer time to peak. A peak concentration of 1,660 ng/mL was obtained in less than an hour for an 80 mg dose.

Distribution

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

Elimination

Caffeine is cleared rapidly 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 1- methylxanthine and 1-methyluric acid.

Excretion

Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug. The plasma half-life is about 3 hours.

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, aspirin, caffeine, and codeine or butalbital alone have not been conducted.

Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic.

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/m² 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/m² basis) for two years.

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/m² 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/m² 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.

Aspirin is not mutagenic in the Ames Salmonella assay; however, aspirin did induce chromosome aberrations in cultured human fibroblasts.

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, aspirin, caffeine, and codeine on fertility. There are also no data on butalbital alone or codeine alone.

Aspirin inhibits ovulation in rats.

Caffeine (as caffeine base) administered to male rats at 50 mg/kg/day subcutaneously (2 times the MHDD on a mg/m² 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.

14 CLINICAL TRIALS

Evidence supporting the efficacy of Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules is derived from 2 multi-clinic trials that compared patients with tension

headache randomly assigned to 4 parallel treatments: Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules, codeine, Butalbital, Aspirin, and Caffeine capsules, USP, and placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules proved statistically significantly superior to each of its components (butalbital, aspirin, caffeine, and codeine) and to placebo on measures of pain relief.

Evidence supporting the efficacy and safety of Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP Capsules in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because codeine and butalbital are habit-forming and potentially abusable.

16 HOW SUPPLIED/STORAGE AND HANDLING

Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP have a plain blue opaque cap with a yellow opaque body imprinted with "B 074" in black ink. They are available in bottles of 100 capsules [NDC 79739-6094-1] and 500 capsules [NDC 79739-6094-5].

Store and Dispense

Store below 25°C (77°F) in a tight, light-resistant container. Protect from moisture. Store Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP securely and dispose of properly [see *Patient Counseling Information (17)*].

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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, 5.5), Drug Abuse and Dependence (9.2)*]. Inform patients that leaving Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP by following these four steps:

- Mix Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP (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;
- Delete 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP with others and to take steps to protect Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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.

Risks from Concomitant Use with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. 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 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is 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 Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP to monitor 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 (5.8); Adverse Reactions (6.2)*].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP [see *Drug Interactions* (7)].

Important Administration Instructions

Instruct patients how to properly take Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. [see *Dosage and Administration* (2.3)]. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP without first discussing a tapering plan with the prescriber [see *Dosage and Administration* (2.4)].

Driving or Operating Heavy Machinery

Inform patients that Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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* (5.18)].

Risk of Bleeding

Inform patients about the signs and symptoms of bleeding. Tell patients to notify their physician if they are prescribed any drug which may increase risk of bleeding.

Counsel patients who consume three or more alcoholic drinks daily about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin [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), *Clinical Pharmacology* (12.2)].

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* (5.11)].

Hypotension

Inform patients that Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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* (5.12)].

Anaphylaxis

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

Aspirin Allergy

Patients should be informed that Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP contains aspirin and should not be taken by patients with an aspirin or NSAIDs allergy [see *Warnings and Precautions* (5.22)].

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP can (or may) cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy. Inform pregnant women to avoid use of aspirin and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [see *Warnings and Precautions* (5.17) and *Use in Specific Populations* (8.1)].

Lactation

Advise nursing mothers to carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [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 *Use in Specific Populations* (8.3)].

Serious Skin Reactions, including DRESS

Advise patients to stop taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [see *Warnings and Precautions* (5.21)].

Manufactured by:

LGM Pharma Solutions, LLC, Irvine, CA 92614

6094-PD

Rev 07/2024

MEDICATION GUIDE

Medication Guide Butalbital, Aspirin, Caffeine, and Codeine Phosphate, USP capsules, CIII
Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is: <ul style="list-style-type: none">• 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP:

- **Get emergency help or call 911 right away if you take too much Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP (overdose).** When you first start taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. They could die from taking it. Selling or giving away Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP is against the law.
- Store Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Important Information Guiding Use in Pediatric Patients:

- Do not give Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP to a child younger than 12 years of age.
- Do not give Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
- Avoid giving Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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 give Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP to a child or teenager with a viral illness. Reye's syndrome, a life-threatening condition, can happen when aspirin (an ingredient in Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP) is used in children and teenagers who have certain viral illnesses.

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

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- known allergy to nonsteroidal anti-inflammatory drug products (NSAIDs)
- a rare disorder in which your blood doesn't clot normally (hemophilia)

Before taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, 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:

- noticing your pain getting worse. If your pain gets worse after you take Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP, do not take more of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.
- **are pregnant or planning to become pregnant.** Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP may harm your baby. Use of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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. Taking NSAID-containing products like Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- **are breastfeeding.** Not recommended; may harm your baby.
- **develop any type of rash or fever.** Contact your healthcare provider as soon as possible and stop taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.
- are living in a household where there are small children or someone who has abused street or prescription drugs
- **are taking prescriptions or over-the-counter medicines, vitamins, or herbal supplements.** Taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP with certain other medicines can cause serious side effects that could lead to death.

When taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP:

- Do not change your dose. Take Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP for a few days. You may have some Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP.
- Take your prescribed dose of 1 or 2 capsules every 4 hours at the same time every day as needed for pain. 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, Aspirin, Caffeine, and Codeine

Phosphate Capsules, USP regularly, do not stop taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP without talking to your healthcare provider.

- Dispose of expired, unwanted, or unused Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP DO NOT:

- Drive or operate heavy machinery, until you know how Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP affects you. Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP may cause you to overdose and die.

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

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, rash, or fever. 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, lightheadedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- If you are a nursing mother taking Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP 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, Aspirin, Caffeine, and Codeine Phosphate Capsules, USP. Call your healthcare provider 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.

Manufactured by:
LGM Pharma Solutions, LLC
Irvine, CA 92614

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

6094-PD

Rev 07/2024

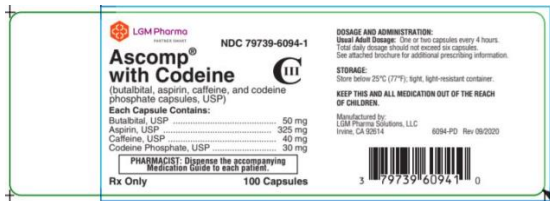
PRINCIPAL DISPLAY PANEL

NDC 79739-6094-1

Ascomp
with Codeine CIII

(butalbital, aspirin, caffeine, and codeine phosphate capsules, USP)

Rx Only 100 Capsules



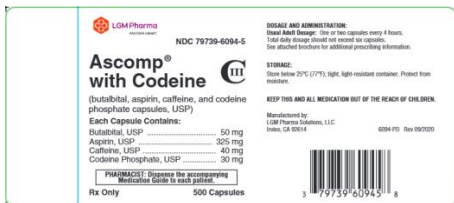
PRINCIPAL DISPLAY PANEL

NDC 79739-6094-5

Ascomp
with Codeine CIII

(butalbital, aspirin, caffeine, and codeine phosphate capsules, USP)

Rx Only 500 Capsules



ASCOMP WITH CODEINE

butalbital, aspirin, caffeine, and codeine phosphate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:79739-6094
Route of Administration	ORAL	DEA Schedule	CIII
Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
BUTALBITAL (UNII: KH50A24JK) (BUTALBITAL - UNII:KH50A24JK)	BUTALBITAL	50 mg	
ASPIRIN (UNII: R16C05Y76E) (ASPIRIN - UNII:R16C05Y76E)	ASPIRIN	325 mg	
CAFFEINE (UNII: 3G6A5W338E) (CAFFEINE - UNII:3G6A5W338E)	CAFFEINE	40 mg	
CODEINE PHOSPHATE (UNII: GSLO5Y1MN6) (CODEINE ANHYDROUS - UNII:UX60W2V7J)	CODEINE PHOSPHATE	30 mg	
Inactive Ingredients			

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY35J)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
D&C YELLOW NO. 10 (UNII: 355W6USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XDA)	
GELATIN (UNII: 2G86QN327L)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
STEARIC ACID (UNII: 4ELVZ765AP)	
TALC (UNII: 75EV74R1U)	
TITANIUM DIOXIDE (UNII: 15F1X9VZJP)	

Product Characteristics

Color	yellow (Yellow Body) , blue (Blue Cap)	Score	no score
Shape	CAPSULE (Hard Gelatin Capsule)	Size	14mm
Flavor		Imprint Code	B;074
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:79739-6094-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	07/24/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075231	11/30/2001	

Labeler - LGM PHARMA SOLUTIONS, LLC (117549198)

Establishment

Name	Address	ID/FEI	Business Operations
LGM Pharma Solutions, LLC		117549200	analysis(79739-6094) , label(79739-6094) , manufacture(79739-6094) , pack(79739-6094)

Revised: 7/2024

LGM PHARMA SOLUTIONS, LLC