PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

[N]APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ¼

[N]APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ½

Butalbital, Acetylsalicylic acid, Caffeine and Codeine Phosphate Capsules

50 mg / 330 mg / 40 mg / 15 mg

50 mg / 330 mg / 40 mg / 30 mg

USP

Combination Analgesic

APOTEX INC

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Toronto, Ontario
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Date of Preparation:
January 15, 2025

Submission Control No: 292215

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Capsule/ 50 mg / 330 mg / 40 mg / 15 mg 50 mg / 330 mg / 40 mg / 30 mg	FD&C Blue #1, FD&C Red #3, gelatin, microcrystalline cellulose, pregelatinized starch, stearic acid, talc and titanium dioxide.

INDICATIONS AND CLINICAL USE

Adults

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE (butalbital-acetylsalicylic acid-caffeine-codeine) is indicated for the relief of tension-type headache.

Evidence supporting the efficacy and safety of butalbital-acetylsalicylic acid-caffeine-codeine capsules in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because repeated use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE may cause medication overuse headaches and codeine and butalbital are habit-forming and potentially abusable (see **WARNINGS and PRECAUTIONS, Dependence/Tolerance**).

Geriatrics (> 65 years of age)

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, concomitant disease or other drug therapy (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Pediatrics (< 18 years of age)

Regardless of clinical setting, codeine (including APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**; also **DOSAGE AND ADMINISTRATION**).

The safety and efficacy of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE has not been studied in the pediatric population. Therefore the use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substances acetylsalicylic acid (ASA), caffeine, codeine or other opioid analgesics, butalbital, or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type)
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- Patients with mild pain that can be managed with other pain medications
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale
- Patients with acute alcoholism, delirium tremens, and convulsive disorders
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy)
- Women who are breast-feeding, pregnant or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS**, and **WARNINGS AND PRECAUTIONS**).
- Pediatric patients (<18 years of age) who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome
- Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage)
- Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to ASA or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients
- Peptic ulcer or other serious gastrointestinal lesions
- Patients with porphyria
- In patients with a history of abuse or overdosage due to alcohol, hypnotics, analgesics and psychotropic drugs
- Pneumonia

- Acute asthma attack
- Coma
- Patients known to be CYP2D6 ultra-rapid metabolizers for whom there is an increased risk of developing symptoms of opioid toxicity, even at commonly prescribed doses (see **WARNINGS AND PRECAUTIONS**)

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE (butalbital-acetylsalicylic acid-caffeine-codeine) capsules should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE or following a dose increase.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental ingestion of even one dose of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE especially by children, can result in a fatal overdose of codeine (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

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 (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Risk in Pregnancy: APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is contraindicated for use during pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see WARNINGS AND PRECAUTIONS). During the third trimester there is risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see also WARNINGS AND PRECAUTIONS, Risk of Death in Ultra-Rapid Metabolizers of Codeine, Neonatal Opioid Withdrawal Syndrome (NOWS), and Special Populations, Pregnant Women).

General
Patients should be instructed not to give APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE (butalbital-acetylsalicylic acid-caffeine-codeine-) capsules to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be stored securely to avoid theft or misuse.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further opioid dose increase can occur at particularly high doses. If hyperalgesia occurs with APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE use, a change in medication may be required (see **WARNINGS AND PRECAUTIONS, Opioid Induced Hyperalgesia**).

Because of its ASA content, APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be used with caution in patients with a history of bleeding tendencies, in patients on anticoagulant therapy and in patients with underlying hemostatic defects and with extreme caution in patients with peptic ulceration.
Thrombocytopenia has been reported in association with the use of ASA, and may be the underlying cause of the increased risk of bleeding, intracerebral hemorrhage and hemorrhagic stroke observed in patients treated with ASA as an antiplatelet therapy.

ASA administered pre-operatively may prolong the bleeding time.

Therapeutic doses of ASA can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to ASA, although a specific history of allergy may be lacking.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to ASA is particularly likely in patients with nasal polyps and relatively common in those with asthma.

A possible association between Reye's syndrome and the use of salicylates has been suggested but not established. Reye's syndrome has also occurred in many patients not exposed to salicylates. However, caution is advised when prescribing salicylate-containing medications for young adults with influenza or chickenpox.

Long-term use of preparations containing barbiturates and/or codeine may lead to habituation and physical dependence. Butalbital-acetylsalicylic acid-caffeine-codeine capsules, because of its codeine and butalbital content, should be avoided in patients with head injury, in whom a depressed CNS is suspected. Similarly, it should not be used in patients with actual or a predisposition towards respiratory depression.

Risk of Death in Ultra-Rapid Metabolizers of Codeine:

Codeine is metabolized by the liver enzyme CYP2D6 into morphine, its active metabolite. Some individuals may be extensive or ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labelled dosage regimens, individuals who are extensive or ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. If the patient is a CYP2D6 ultra-rapid metabolizer and a nursing mother, higher levels of morphine may be present in breast milk and may result in symptoms of opioid toxicity in the infant, which may be fatal. Therefore, the use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is contraindicated in patients known to be ultra-rapid metabolizers, as well as in nursing mothers (see **CONTRAINDICATIONS;** See also **Labour, Delivery and Nursing Women** in **Special Populations**).

The prevalence of this CYP2D6 phenotype varies widely by ethnic group and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Cases of acute pancreatitis have been reported with the use of codeine and should therefore be considered as a possible side effect of this compound.
Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Abuse and Misuse
Like all opioids, codeine is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as codeine should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is intended for oral use only. The capsules should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Carcinogenesis and Mutagenesis
See **TOXICOLOGY** section.

Cardiovascular

Codeine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

The use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE in patients with circulatory shock should be avoided as codeine may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance

Codeine
As with other opioids, tolerance and physical dependence may develop upon repeated administration of butalbital-acetylsalicylic acid-caffeine-codeine capsules and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged opioid therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).**

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

Use in Drug and Alcohol Addiction
Codeine is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to butalbital-acetylsalicylic acid-caffeine-codeine capsules ; extreme caution and awareness is warranted to mitigate the risk.

Endocrine
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.

Gastrointestinal Effects
Codeine and other morphine-like opioids have been shown to decrease bowel motility. The codeine component of butalbital-acetylsalicylic acid-caffeine-codeine capsules may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Monitoring and Laboratory Tests
Pregnancy: APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is contraindicated for use in pregnancy. If APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on butalbital-acetylsalicylic acid-caffeine-codeine capsules be closely monitored for amniotic fluid volume since butalbital-acetylsalicylic acid-caffeine-codeine capsules may result in reduction of amniotic fluid volume and even oligohydramnios (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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.

Use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is

contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Codeine should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, gabapentinoids, baclofen, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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

Advise both patients and caregivers about the risks of respiratory depression and sedation when butalbital-acetylsalicylic acid-caffeine-codeine capsules 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**).

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation,** and **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury: The respiratory depressant effects of codeine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, codeine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, butalbital-acetylsalicylic acid-caffeine-codeine capsules must be used with

extreme caution and only if it is judged essential (see **CONTRAINDICATIONS).**

Butalbital-acetylsalicylic acid-caffeine-codeine capsules is associated with exacerbation of headache when used too frequently (medication overuse headaches) in susceptible patients. Repeated use of butalbital-acetylsalicylic acid-caffeine-codeine capsules can lead to "rebound" headaches as each dose wears off. With repeated doses physical and psychological dependence can develop. In addition to dependence, butalbital-containing products can lead to tolerance, and at higher doses can produce withdrawal symptoms after discontinuation (see **WARNINGS AND PRECAUTIONS, Dependence/Tolerance, *Butalbital***).

Opioid Induced Hyperalgesia: Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful stimuli (allodynia), in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

Serotonin Toxicity/Serotonin Syndrome:

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with codeine, particularly during combined use with other serotonergic drugs (see **DRUG INTERACTIONS**).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g., tachycardia, flushing) and altered mental state (e.g., anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **DRUG INTERACTIONS**). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Peri-Operative Considerations

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative

pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with butalbital-acetylsalicylic acid-caffeine-codeine capsules for at least 24 hours before the operation and butalbital-acetylsalicylic acid-caffeine-codeine capsules should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if butalbital-acetylsalicylic acid-caffeine-codeine capsules is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Codeine and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Butalbital-acetylsalicylic acid-caffeine-codeine capsules should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Butalbital-acetylsalicylic acid-caffeine-codeine capsules may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of codeine with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

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 from opioid use, 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. Butalbital-acetylsalicylic acid-caffeine-codeine capsules because of the codeine component should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS)**.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of codeine the risk is greatest during the initiation of therapy or following a dose increase.

Patients should be closely monitored for respiratory depression when initiating therapy with butalbital-acetylsalicylic acid-caffeine-codeine capsules and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of butalbital-acetylsalicylic acid-caffeine-codeine capsules are essential. Overestimating the codeine dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**).

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

Sleep Apnea: 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 butalbital-acetylsalicylic acid-caffeine-codeine capsules dosage using best practices for opioid taper (see **DOSAGE AND ADMINISTRATION**).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with butalbital-acetylsalicylic acid-caffeine-codeine capsules as in these patients, even usual therapeutic doses of codeine may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Sexual Function/Reproduction
Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS, Post-Marketing Experience**)

Skin

Serious skin reactions: Use of some NSAIDs, such as butalbital-acetylsalicylic acid-caffeine-codeine capsules , have been associated with rare post-market cases of serious, fatal or otherwise life-threatening skin reactions, including:

- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome,
- toxic epidermal necrolysis,
- exfoliative dermatitis and
- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

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, and 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.

Special Populations

Special Risk Groups: Because of the codeine component, butalbital-acetylsalicylic acid-caffeine-codeine capsules should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture. In addition, butalbital-acetylsalicylic acid-caffeine-codeine capsules should be administered with caution in patients with severe impairment of renal or hepatic function, coagulation disorders, head injuries, elevated intracranial pressure, acute abdominal conditions, peptic ulcer, or in osteomalacia or osteoporosis.

Pregnant Women: Studies in humans have not been conducted. butalbital-acetylsalicylic acid-caffeine-codeine capsules crosses the placental barrier and is contraindicated in pregnant women.

Animal reproduction studies have not been conducted with butalbital-acetylsalicylic acid-caffeine-codeine capsules .

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is contraindicated during pregnancy (see **CONTRAINDICATIONS**) because the codeine component of butalbital-

acetylsalicylic acid-caffeine-codeine capsules significantly increases the rate of malformations if used in the first trimester of pregnancy (deformities of the respiratory tract, slight increase in cleft lip and palate). In the last trimester of pregnancy, codeine may cause withdrawal symptoms in the neonate (also in the foetus if therapy is discontinued before birth).

Due to the NSAID component in butalbital-acetylsalicylic acid-caffeine-codeine capsules , during the third trimester of pregnancy there are also risks of premature closure of the ductus arteriosus and the potential to prolong parturition. During the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) there is risk of possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

Published studies and postmarketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

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. 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 after careful consideration of the benefit-risk, butalbital-acetylsalicylic acid-caffeine-codeine capsules treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if butalbital-acetylsalicylic acid-caffeine-codeine capsules treatment extends beyond 48 hours and that butalbital-acetylsalicylic acid-caffeine-codeine capsules treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenesis period.

Although butalbital-acetylsalicylic acid-caffeine-codeine capsules was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The

infant was born 8 weeks prematurely to a woman who had taken an average of 90 butalbital-acetylsalicylic acid-caffeine-codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that ASA taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, ASA administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Therapeutic doses of ASA in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of ASA in high doses may prolong pregnancy and delivery.

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

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is contraindicated in nursing women and during labour (or in case of risk of premature labour) and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if butalbital-acetylsalicylic acid-caffeine-codeine capsules is used in this population. Ingestion of ASA prior to delivery may prolong delivery or lead to bleeding in the mother or neonate.

In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. **However, some women are ultra-rapid metabolisers of codeine (**see **CONTRAINDICATIONS, Ultra-Rapid Metabolisers of Codeine). These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breast-fed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death in nursing infants.**

Since there is a risk of infant exposure to codeine and morphine through breast milk, APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is contraindicated in breast-feeding. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about any use of codeine during breast-feeding.

ASA, caffeine and barbiturates are excreted into human breast milk, but the significance of their effects on nursing infants is not known.

Pediatrics (< 18 years of age): Regardless of clinical setting, codeine (including APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **INDICATIONS**, and **DOSAGE AND ADMINISTRATION**). The safety and efficacy of butalbital-acetylsalicylic acid-caffeine-codeine capsules have not been studied in the pediatric population. Therefore, use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is not recommended in patients over 12 and under 18 years of age.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Patients with Hepatic Impairment:
APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be prescribed with caution in patients with severe impairment of hepatic function.

Patients with Renal Impairment:
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.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be prescribed with caution in patients with severe impairment of renal function.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE (butalbital-acetylsalicylic acid-caffeine-codeine) capsules are similar to those of other opioid-containing analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed adverse effects associated with the use of butalbital-acetylsalicylic acid-caffeine-codeine capsules and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness and dizziness. Less frequent adverse

reactions are constipation, rash, miosis, lightheadedness and gastrointestinal disturbances including nausea, vomiting and flatulence. Several cases of dermatological reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme have been reported.

Of the 382 patients treated with butalbital-acetylsalicylic acid-caffeine-codeine capsules in controlled clinical trials, three (0.8%) discontinued treatment with butalbital-acetylsalicylic acid-caffeine-codeine capsules because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following table summarizes the incidence rates of the treatment emergent adverse events reported by at least 1% of the butalbital-acetylsalicylic acid-caffeine-codeine capsules treated patients in controlled clinical trials comparing butalbital-acetylsalicylic acid-caffeine-codeine capsules to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

Table 1: Adverse Events Reported by at Least 1% of Butalbital-Acetylsalicylic acid-Caffeine-Codeine Capsules Treated Patients during Placebo Controlled Clinical Trials

Incidence Rate of Adverse Events		
Body System/Adverse Event	**Butalbital-acetylsalicylic acid-caffeine-codeine capsules (N = 382)**	**Placebo (N = 377)**
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0.0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and

respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse effects occur less frequently with opioid analgesics and include those reported in butalbital-acetylsalicylic acid-caffeine-codeine capsules clinical trials, whether related or not to the active components, including codeine.

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.

Post-Marketing Experience

Voluntary reports of adverse drug events, temporally associated with butalbital-acetylsalicylic acid-caffeine-codeine capsules, that have been received since market introduction and that were not reported in clinical trials by the patients treated with butalbital-acetylsalicylic acid-caffeine-codeine capsules, are listed below. Many or most of these events may have no causal relationship

with the drug and are listed according to body system.

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, hives, rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, DRESS, lichenoid eruption.
Urinary: kidney impairment, urinary difficulty.
Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of butalbital-acetylsalicylic acid-caffeine-codeine capsules. Potential effects of high dosage are listed in the **OVERDOSAGE**.

ASA: occult blood, hemolytic anemia, iron deficiency anemia, dyspepsia, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, nephropathy toxic when taken in high doses for prolonged periods, urine uric acid decreased, hepatitis.
Caffeine: tachycardia, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.
Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.
Butalbital: incoordination, difficulty thinking, poor memory, faulty judgment, decreased attention, emotional lability, exaggeration of personality traits.

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives, gabapentinoids such as gabapentin and pregabalin, baclofen, hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. 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. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Coadministration of codeine with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of ASA, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

The prolonged ingestion of barbiturates gives rise to enzyme induction. This increases the rate of metabolism of certain drugs, including oral anticoagulants and oral contraceptives, thus reducing their effectiveness.

butalbital-acetylsalicylic acid-caffeine-codeine capsules may enhance the effects of:

1. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect if dosage of butalbital-acetylsalicylic acid-caffeine-codeine capsules exceeds maximum recommended daily dosage.

2. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.

3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.

4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.

Butalbital-acetylsalicylic acid-caffeine-codeine capsules may diminish the effects of:

Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. ASA competes with these agents for protein binding sites.

Drug-Laboratory Interactions

ASA may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, aspartate aminotransferase (AST), uric acid, prothrombin time and bleeding time. ASA may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleactic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine may increase serum amylase levels.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

DOSAGE AND ADMINISTRATION

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Children under 12: Regardless of clinical setting, codeine (including APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE) should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see **INDICATIONS**).

Patients should be instructed to seek the advice of a physician if no effective pain relief is achieved after 3 days of treatment.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. The maximum recommended daily dose of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is 6 tablets, which is 180 mg codeine (27 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of butalbital-acetylsalicylic acid-caffeine-codeine capsules (see **DOSAGE AND ADMINISTRATION, Adjustment or reduction of Dosage).**

Dosing Considerations

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE (butalbital-acetylsalicylic acid-caffeine-codeine) capsules should be used with caution within 12 hours pre-operatively and within the first 12 to 24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, should be prescribed at the lowest effective dose for the shortest period of time. Dosing should be as needed every 4 to 6 hours and not on scheduled intervals. Continuous daily use should be avoided.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is not indicated for rectal administration.

Recommended Dose and Dosage Adjustment

Adults:
1 or 2 capsules at once with a glass of water, followed if necessary, by 1 capsule every 4 to 6 hours, up to 6 capsules daily, or as prescribed.

Geriatrics:
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including butalbital-acetylsalicylic acid-caffeine-codeine capsules. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see

WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Disposal

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be kept in a safe place, out of the sight and reach of children before, during and after use. APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should not be used in front of children, since they may copy these actions.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

The toxic effects of acute overdosage of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE (butalbital-acetylsalicylic acid-caffeine-codeine capsules) are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, ASA. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE overdosage is unlikely.

Symptoms:

1) Acute barbiturate poisoning: drowsiness, confusion and coma, with reduced or absent reflexes; prominent, persistent respiratory depression; hypotension, followed by circulatory collapse and a typical shock-like state in severe intoxication; respiratory complications, renal failure, and, possibly, death.
2) Acute ASA poisoning: principal toxic effects include hyperpnea; hypercapnia; acid-base disturbances with the development of metabolic acidosis, especially in children; and gastrointestinal irritation with vomiting and abdominal pain. Also, acetone odour in breath, tinnitus, sweating, hyperthermia, dehydration, hypoprothrombinemia with spontaneous bleeding, restlessness, delirium, convulsions and coma may occur.

3) Acute caffeine poisoning: insomnia, restlessness, tinnitus and flashes of light; tachycardia and extrasystoles; tremor, delirium and coma, following high doses in the region of 10 g. Death has not been reported with caffeine overdosage.
4) Acute codeine poisoning: Signs and symptoms of codeine overdose include miosis (pinpoint pupils), sedation, hypotension, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, respiratory depression, and death. Nausea and vomiting may be observed. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. Convulsions may occur.

Note: Because large doses of barbiturate alone may cause marked respiratory and CNS depression, an even more profound depressant effect may be expected after an overdosage of butalbital-acetylsalicylic acid-caffeine-codeine capsules.

The dangers of butalbital-acetylsalicylic acid-caffeine-codeine capsules overdosage are increased when the drug is ingested in the presence of alcohol, phenothiazines, minor tranquilizers and/or narcotics.

Treatment:
The management of acute butalbital-acetylsalicylic acid-caffeine-codeine capsules overdosage may involve the treatment of the toxic effects of all its constituents, with the possible exception of caffeine, which is toxic in very high doses only. Generally, it is the management of the barbiturate intoxication, the correction of the acid-base imbalance due to salicylism and the reversal of the effects of codeine which demand most attention. The therapeutic procedures most commonly employed are:

Elimination of the offending drug:
1) Perform gastric lavage followed by the administration of activated charcoal if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. Do not attempt gastric lavage on the unconscious patient unless cuffed endotracheal intubation has been performed to prevent aspiration and pulmonary complications.
2) Catharsis: Following gastric lavage, a saline cathartic (sodium or magnesium sulfate 30 g in 250 mL of water) may be introduced and left in the stomach.
3) Encourage diuresis by administration of i.v. fluids assisted, if necessary, by 100 to 150 mL 25% mannitol solution given slowly i.v. Note: Mannitol should not be mixed with blood in a transfusion set, as red cell crenation and agglutination may occur.
4) Alkalinization of the urine (see caution): i.v. isotonic sodium bicarbonate solution accelerates urinary excretion of barbiturates. Maximum alkalinization may be more successfully attained if the sodium bicarbonate infusion is accompanied by acetazolamide 250 mg given as a single i.v. injection every 6 hours. (Caution: perform urinary alkalinization with care in children).
5) Peritoneal dialysis and hemodialysis have been used with success in acute barbiturate intoxication and may be life-saving. However, before embarking on either method, weigh the risks inherent to these procedures against the risk of not using them at all.

Maintenance of adequate pulmonary ventilation: Respiratory depression is an early and often

profound manifestation of acute barbiturate poisoning. Meticulous attention to this aspect of treatment is essential. Perform pharyngeal and tracheal suction diligently to remove excess mucous secretions. Judicious administration of oxygen is also indicated. However, oxygen without assisted respiration must be used with caution, as its use in hypoventilation hypoxia may result in further respiratory depression and hypercapnia. In more critical cases, endotracheal intubation or tracheotomy, with or without assisted respiration, may be necessary.

Correction of hypotension: Vigorous treatment is essential, as circulatory collapse and renal failure are frequent causes of death.

1) Mild cases: the usual head down position and other supportive measures may be adequate.
2) Severe cases: Vasopressors (dopamine, levarterenol) may be given i.v. with the usual precautions and serial blood pressure monitoring.

Narcotic antagonism: naloxone injection may reverse the respiratory depression caused by codeine and should be used until respiration improves. 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.

Note: Respiratory depression caused by barbiturates will not respond to narcotic antagonists. Unwitting overdosage with narcotic antagonists may occur in an attempt to reverse respiratory depression caused by mixed barbiturate-codeine intoxication.

Special features due to salicylate overdosage:

1) The prominent features of salicylate intoxication are metabolic acidosis and electrolyte disturbance, and these require evaluation and correction. Sodium bicarbonate 400 mg (5 mEq)/kg as a 1% solution in 5% dextrose water is not only effective in correcting acidosis, but effectively and rapidly accelerates salicylate excretion by the kidneys. The administration of sodium bicarbonate must be carefully monitored with frequent blood pH and plasma CO_2 content determinations, as large amounts of sodium bicarbonate may result in severe alkalosis, particularly in children. THAM, an osmotic alkalinizing diuretic, also greatly increases the excretion of salicylate. This is given as a 0.3 molar solution at a rate not exceeding 5 mL/kg/hour. Potassium deficiency may occur and should be corrected.
2) Treat hyperthermia and dehydration with ice packs and i.v. fluids.
3) Treat hypoprothrombinemia with vitamin K_1 50 mg given daily i.v.
4) Hemodialysis, peritoneal dialysis or exchange transfusion are indicated in very severe salicylate intoxication. However, in butalbital-acetylsalicylic acid-caffeine-codeine capsules overdosage, these measures are indicated mainly for barbiturate intoxication but would be effective for both.

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

General supportive measures:

1) Good nursing care is of prime importance, particularly in the comatose patient, and should include regular observation and accurate recording of the vital signs and depth of coma, maintenance of a free airway, frequent turning, and other routine measures usually adopted with unconscious patients.
2) Careful supervision and recording of fluid intake and output is essential.
3) Take blood samples to determine barbiturate blood concentrations and for electrolyte and other pertinent blood studies.

Toxic and Lethal Doses (for adults):
ASA: toxic blood level greater than 30 mg/100 mL; lethal dose 10 to 30 g
Caffeine: toxic dose greater than 1 g; (25 capsules); lethal dose 6.5 to 10 g
Codeine: toxic dose 240 mg (8 capsules); lethal dose 0.5 to 1 g
Butalbital: toxic dose 1 g (20 capsules); lethal dose 2 to 5 g

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ASA is a salicylate that binds to the cyclooxygenase enzyme leading to a reduction in prostaglandin activity.

Caffeine is a CNS stimulant with primary effects on adenosine receptors.

Codeine is an opiate which acts on the CNS through agonistic action on opiate receptors.

Butalbital is a short to intermediate-acting barbiturate which is thought to act on the CNS through enhanced gamma-aminobutyric acid (GABA) binding to GABA A receptors.

Pharmacodynamics of Codeine

Central Nervous System:
Codeine produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Codeine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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 origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of codeine overdose.

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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:
Codeine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System:
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System:
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics

Acetylsalicylic acid (ASA)
The systemic availability of ASA 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 ASA prior to absorption.

During the absorption process and after absorption, ASA 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% to 80% of the salicylic acid and its metabolites are loosely bound to plasma proteins.

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 ASA 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.

The biotransformation of ASA occurs primarily in the hepatocytes. The major metabolites are salicyluric acid (75%), the phenolic and acyl glucuronides of salicylate (15%), and gentisic and

gentisuric acid (1%).

Caffeine
Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared rapidly through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion results in about equal amounts of 1-methylxanthine and 1-methyluric acid. Of the 70% of the dose that has been recovered in the urine, only 3% was unchanged drug.

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

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide-conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours. Patients who lack functional CYP2D6 genes do not metabolize codeine to morphine and may experience less analgesic effect.

Butalbital
Butalbital is well absorbed from the gastrointestinal tract and 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.

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. The elimination half-life of butalbital is about 61 hours (range: 35 to 88 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.

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% - 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.

Special Populations and Conditions

Pediatrics: Individuals under 18 years of age should not take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE capsules.

Geriatrics:
Clinical studies of butalbital-acetylsalicylic acid-caffeine-codeine 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.

Hepatic Impairment:
APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be prescribed with caution in patients with severe impairment of hepatic function.

Renal Impairment:
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.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be prescribed with caution in patients with severe impairment of renal function.

STORAGE AND STABILITY

Store at room temperature between 15-30°C.

Keep out of reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms:

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ¼
Capsules:
Hard gelatin oblong capsule, white opaque body with blue opaque cap, printed with "FIORINAL-C ¼" in black ink.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ½
Capsules:
Hard gelatin oblong capsule, light blue opaque body with blue opaque cap, printed with "FIORINAL-C ½" in black ink.

Composition:

Each APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ¼ capsule contains the following active ingredients: butalbital USP 50 mg, caffeine USP 40 mg, ASA USP 330 mg, codeine phosphate USP 15 mg. Nonmedicinal ingredients: FD&C Blue #1, FD&C Red #3, gelatin, microcrystalline cellulose, pregelatinized starch, stearic acid, talc and titanium dioxide.

Each APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ½ capsule contains the following active ingredients: butalbital USP 50 mg, caffeine USP 40 mg, ASA USP 330 mg, codeine phosphate USP 30 mg. Nonmedicinal ingredients: FD&C Blue #1, FD&C Red #3, gelatin, microcrystalline cellulose, pregelatinized starch, stearic acid, talc and titanium dioxide.

Packaging:

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ¼ capsules: Bottles of 100.
APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ½ capsules: Bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

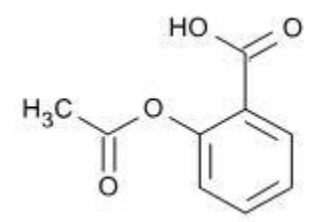
Acetylsalicylic acid (ASA)

Proper name: Acetylsalicylic acid (ASA)

Chemical name: benzoic acid, 2-(acetyloxy)-

Molecular formula and molecular mass: $C_9H_8O_4$, 180.16 g/mol

Structural formula:



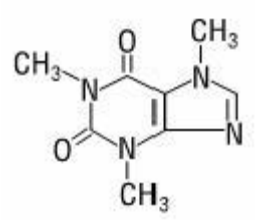
Caffeine

Proper name: Caffeine

Chemical name: 1,3,7-trimethylxanthine

Molecular formula and molecular mass: $C_8H_{10}N_4O_2$, 194.19 g/mol

Structural formula:



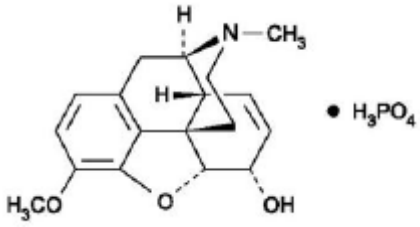
Codeine

Proper name: Codeine phosphate

Chemical name: 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate

Molecular formula and molecular mass: $C_{18}H_{24}NO_7P$ anhydrous molecular weight 397.37 g/mol

Structural formula:



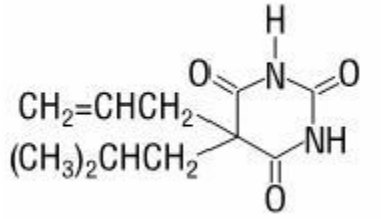
Butalbital

Proper name: Butalbital

Chemical name: 5-allyl-5-isobutylbarbituric acid

Molecular formula and molecular mass: $C_{11}H_{16}N_2O_3$, 224.26 g/mol

Structural formula:



CLINICAL TRIALS

Evidence supporting the efficacy of butalbital-acetylsalicylic acid-caffeine-codeine capsules is derived from 2 multi-clinic trials that compared patients with tension-type headache randomly assigned to 4 parallel treatments: butalbital-acetylsalicylic acid-caffeine-codeine capsules, codeine, butalbital-acetylsalicylic acid-caffeine capsules , 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-acetylsalicylic acid-caffeine-codeine capsules proved statistically significantly superior to each of its components (butalbital-acetylsalicylic acid-caffeine capsules, codeine) and to placebo on measures of pain relief.

TOXICOLOGY

Teratogenicity:
A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

Mutagenicity:
Codeine is not mutagenic *in vitro* or *in vivo*.

Carcinogenicity:
Codeine did not show carcinogenic potential in 2 year rat and mouse studies. Long-term studies have been conducted in mice and rats with ASA, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis or impairment of fertility.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N] APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ¼

[N] APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ½

Butalbital, Acetylsalicylic acid, Caffeine and Codeine Phosphate Capsules

USP

Read this carefully before you start taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

Serious Warnings and Precautions

- **Even if you take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE it must be swallowed whole. Do not cut, break, crush, chew, or dissolve the capsules. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. They could die from taking it. If a person has not been prescribed APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, taking even one dose can cause a fatal overdose. This is especially true for children.**

Pregnancy:

DO NOT take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-

CODEINE if you are pregnant.

Medicines like APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE may cause harm to you and your baby. If your doctor feels it is necessary for you to take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE during pregnancy, your doctor will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE during this time.

- **If you took APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.

Taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE 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.

What is APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE used for?

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, is used in adults for the relief of tension-type headache.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is recommended for adults 18 years and older.

How does APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE work?

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE consists of acetylsalicylic acid (ASA), caffeine, codeine and butalbital.

ASA reduces pain, fever and inflammation. Caffeine is a mild stimulant which may enhance pain-relieving effects. Codeine is an opioid that relieves pain by acting on specific nerve cells of the spinal cord and brain. Butalbital is a sedative that causes relaxation. This combination is used to relieve tension-type headaches.

What are the ingredients in APO-BUTALBITAL-ACETYLSALICYLIC ACID-

CAFFEINE-CODEINE?

Medicinal ingredients: ASA (acetylsalicylic acid), caffeine, codeine and butalbital.

Non-medicinal ingredients: FD&C Blue #1, FD&C Red #3, gelatin, microcrystalline cellulose, pregelatinized starch, stearic acid, talc and titanium dioxide.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE comes in the following dosage forms:
APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ¼ capsules contain 330 mg ASA, 40 mg caffeine, 15 mg codeine phosphate and 50 mg butalbital.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE- C ½ capsules contain 330 mg ASA, 40 mg caffeine, 30 mg codeine phosphate and 50 mg butalbital.

Do not use APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE if:

- your doctor did not prescribe it for you
- you are allergic to ASA, caffeine, codeine, butalbital or any of the other ingredients in APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE capsules (see **What are the ingredients in APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE?**)
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you are pregnant, planning to become pregnant or you are in labour
- you are breastfeeding. The use of codeine-containing products while breast-feeding may harm your baby. If you breastfeed and take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, seek immediate medical care for your baby if they are overly drowsy, sedated, have difficulty breast-feeding, have breathing difficulties, and are floppy (have decreased muscle tone). This is very serious for the baby and can lead to death. Tell the baby's doctor that you are breastfeeding and took APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

- you are under 12 years old
- you are less than 18 years old and are having (or have recently had) your tonsils or adenoids removed because of frequent interruption of breathing during sleep
- have a condition that predisposes to bleeding such as hemophilia, hypoprothrombinemia, von Willebrand's disease, thrombocytopenia, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage
- have nasal polyps, allergic reaction or bronchospastic reactivity to ASA or other nonsteroidal anti-inflammatory drugs (NSAIDs)
- have stomach ulcers or other serious stomach or bowel sores
- have a disease called porphyria
- have a history of drug abuse or drug overdose due to alcohol, sleeping pills, drugs to treat pain or any other prescription or illegal drugs
- have pneumonia (a lung infection)
- have been told by your doctor that you break down codeine rapidly. This can lead to codeine overdose even at the usual adult dose.
- APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is not recommended in children less than 18 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- are allergic to ASA as it can cause anaphylactic shock and other severe allergic reactions
- have nasal polyps or asthma
- have a history of blocked bowels, stomach ulcers, sores in your stomach or bowel or any other serious stomach problems
- have a history of bleeding
- will be having surgery
- have a blood clotting disorder or are taking blood thinners
- have recently suffered a head injury or elevated pressure in your brain
- have problems with your thyroid gland
- have narrowing of the urethra caused by injury or disease
- have Addison's disease
- have an enlarged prostate gland
- have softening or weakening of bones or osteoporosis
- have any allergies to any medicines, food, dyes or preservatives
- have the flu, or chickenpox

- suffer from migraines
- are pregnant, planning on becoming or become pregnant while taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.
- have reacted strongly to other codeine-containing drugs in the past (i.e. got sleepy, confused and/or had trouble breathing) even when taking the dose recommended by your doctor.

Other warnings you should know about:

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is not recommended for anyone who has or is at risk for breathing problems such as:

- lung infections, or respiratory conditions
- neuromuscular disorders
- severe heart problems
- recent multiple traumas or extensive surgical procedures

Sleep Apnea: the codeine in APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

Serious Skin Reactions: In rare cases, serious or life-threatening skin reactions listed below have been reported with some NSAIDs, such as APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome (SJS),
- toxic epidermal necrolysis (TEN),
- exfoliative dermatitis and
- erythema multiforme

You may be at a greater risk of experiencing a serious skin reaction usually during the first month of treatment. See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Some people metabolize codeine at a much faster rate than the general population, which may lead to accidental overdose, if this should happen to you, seek help immediately (see Overdose, for symptoms of overdose and what to do if it happens). If you know that you metabolize codeine rapidly, tell your doctor BEFORE starting this medication.

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE is a controlled medication. Butalbital and codeine are both habit-forming (tolerance, mental and physical

dependence) and potentially abusable. Some patients, particularly those who have abused drugs in the past, may have a higher risk of abusing or developing an addiction while taking barbiturate- or opioid-containing products, such as APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. Physical dependence may lead to withdrawal side effects when you stop taking this medicine. Continuous daily use of APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should be avoided as medication overuse (rebound) headaches may result in addition to the tolerance and dependence risks. Patients should take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Reye's syndrome: ASA may increase the risk of Reye's syndrome, a rare but often fatal condition. Caution should be used in administering ASA-containing medications to young adults who have fever, flu or chicken pox. APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should not be administered to children.

Medical tests: Before you have any medical tests done, tell the person in charge that you are taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. ASA and codeine may interfere with the results of certain tests done in blood and urine.

Testing and check-ups: Your healthcare professional will regularly monitor your health. This includes monitoring for signs of:

- misuse and abuse;
- sleep apnea (a sleep disorder which causes pauses in breathing or shallow breathing while sleeping);
- respiratory depression and sedation (e.g., slow, shallow, or weak breathing).

Pregnancy, nursing, labour and delivery: Do not use APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting

- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

Serotonin Toxicity or Serotonin Syndrome: APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE can cause serotonin toxicity, also known as Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Worsened Pain: Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia), even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your doctor if you notice a change like this in your pain while you are taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose

- other sedative drugs which may enhance the drowsiness caused by APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- triptans used to treat migraines (e.g. oxitriptan)
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medications (such as beta blockers)
- St. John's Wort
- warfarin (such as Coumadin®) and other anticoagulants (used for prevention or treatment of blood clots)
- drugs used to treat panic attacks and seizures
- corticosteroids
- oral drugs to treat diabetes and/or insulin
- drugs used to suppress the immune system such as 6-mercaptopurine and methotrexate
- NSAIDs (non-steroidal anti-inflammatory drugs) to treat pain such as ibuprofen and naproxen
- tranquilizers
- drugs used to treat gout such as probenecid and sulfinpyrazone
- birth control pills

How to take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE:

Swallow whole. Do not cut, break, crush, chew or dissolve the capsules. This can be dangerous and can lead to death or seriously harm you.

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest effective dose for the shortest period of time that works to control your pain. It is recommended that you only take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE for up to 3 days. If you need to take APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Take 1 or 2 capsules at once with a glass of water, followed if necessary, by 1 capsule every 4 to 6 hours. Do not take more than 6 capsules daily or as prescribed.

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE comes as a capsule to take by mouth.

Review your pain regularly with your doctor to determine if you still need APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. Be sure to use APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE only for the condition for which it was prescribed.

Let your doctor know rapidly if no effective pain relief is achieved after 3 days of treatment.

If your pain increases or you develop any side effect as a result of taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, tell your doctor immediately.

Stopping your Medication

If you have been taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you

restart at the last dose you took before you slowly stopped taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

Refilling your Prescription for APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE:

A new written prescription is required from your doctor each time you need more APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your tension headaches.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE?

These are not all the possible side effects you may feel when taking APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Lightheadedness
- Insomnia
- Dizziness

- Fainting
- Nausea, vomiting, or a poor appetite
- Indigestion and/or stomach pain
- Dry mouth
- Headache
- Difficulty thinking
- Poor memory and judgement
- Decreased attention
- Problems with vision
- Small pupils
- Fast or irregular heart beat
- Irritability
- Mood swings exaggeration of personality traits
- Weakness, uncoordinated muscle movement
- Tremor
- Skin rash and itching
- Sweating
- Constipation and gas
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory Depression: Slow, shallow or weak breathing.			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Low Blood Pressure: dizziness, fainting, light-headedness.	√		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			√
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine			√
UNCOMMON **Reye's syndrome:** rash on the palms of hands and feet, severe vomiting, high fever, weakness, confusions, headache, fast breathing leading to unresponsiveness and death			√
Allergic Reaction: itching, rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
UNKNOWN **Pancreatitis:** severe stomach pain with radiation through to the back, nausea and vomiting		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Anemia: fatigue, breathing difficulties, irregular heart beat or pale skin	√		
Stomach ulcer: heartburn, long lasting stomach pain, loss of appetite and weight loss		√	
Prolonged bleeding time	√		
Hepatitis: loss of appetite, dark urine, yellowing of eyes and skin		√	
Blood in the stool		√	
Sleep Apnea: breathing stops for short periods during sleep		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE in a secure place to prevent theft, misuse or accidental exposure.**
- Store your APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE capsules at room temperature (between 15-30°C).

- **Keep APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE, get emergency help right away.**

Disposal:

APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about APO-BUTALBITAL-ACETYLSALICYLIC ACID-CAFFEINE-CODEINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

Last Revised: January 15, 2025