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caffeine, and codeine phosphate capsules for other reasons to monitor for signs of respiratory depression.

- Nursing mothers taking codeine can also have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. Instruct nursing mothers to watch for signs of morphine toxicity in their infants including increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's doctor immediately if they notice these signs and, if they cannot reach the doctor right away, to take the baby to an emergency room or call 911 (or local emergency services).

Laboratory Tests
In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions
The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.
Butalbital, acetaminophen, caffeine, and codeine phosphate capsules may enhance the effects of:
– Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions
Acetaminophen
Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Codeine
Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No adequate studies have been conducted in animals to determine whether acetaminophen, codeine and butalbital have a potential for carcinogenesis or mutagenesis. No adequate studies have been conducted in animals to determine whether acetaminophen and butalbital have a potential for impairment of fertility.

Pregnancy
Teratogenic Effects
Pregnancy Category C: Animal reproduction studies have not been conducted with butalbital, acetaminophen, caffeine, and codeine phosphate capsules. It is also not known whether butalbital, acetaminophen, caffeine, and codeine phosphate capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Butalbital, acetaminophen, caffeine, and codeine phosphate capsules should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects
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.

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

Nursing Mothers
Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine-containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding (see *Warnings-Death Related to Ultra-rapid Metabolism of Codeine to Morphine*).

Barbiturates, acetaminophen, and caffeine are also excreted in breast milk in small amounts. Because of potential for serious adverse reactions in nursing infants from butalbital, acetaminophen, caffeine, and codeine phosphate capsules, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Butalbital, acetaminophen, caffeine, and codeine phosphate capsules are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy (see *Contraindications*).

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

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

ADVERSE REACTIONS
Frequently Observed
The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

Infrequently Observed
All adverse events tabulated below are classified as infrequent.

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

Autonomic Nervous: dry mouth, hyperhidrosis.

Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain, muscle fatigue.

Genitourinary: diuresis.

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

The following adverse reactions have been voluntarily reported as temporally associated with Fiorinal® with Codeine, a related product containing aspirin, butalbital, caffeine, and codeine.

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

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

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

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

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

Urinary: kidney impairment, urinary difficulty.

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

The following adverse drug events may be borne in mind as potential effects of the components of butalbital, acetaminophen, caffeine, and codeine phosphate capsules. Potential effects of high dosage are listed in the **OVERDOSAGE** section.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

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

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

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

DRUG ABUSE AND DEPENDENCE
Controlled Substance
Butalbital, acetaminophen, caffeine, and codeine phosphate capsules are controlled by the Drug Enforcement Administration and is classified under Schedule III.

Abuse and Dependence
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 two-fold. 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.

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

OVERDOSAGE
Following an acute overdose of butalbital, acetaminophen, caffeine, and codeine phosphate capsules, toxicity may result from the barbiturate, the codeine, or the acetaminophen. Toxicity due to the caffeine is less likely, due to the relatively small amounts in this formulation.

Signs and Symptoms
Toxicity from **barbiturate** poisoning include drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock. Toxicity from **codeine** poisoning includes the opioid triad of: pinpoint pupils, depression of respiration, and loss of consciousness. Convulsions may occur.

In **acetaminophen** overdose: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

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

Treatment
A single or multiple drug overdose with butalbital, acetaminophen, caffeine, and codeine phosphate capsules are a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. For respiratory depression due to overdose or unusual sensitivity to codeine, parenteral naloxone is a specific and effective antagonist.

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

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

DOSAGE AND ADMINISTRATION
One or 2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED
Butalbital, acetaminophen, caffeine, and codeine phosphate capsules
Light blue opaque cap with a grey, opaque body. Cap is imprinted in black with "V". Body is imprinted with "3109" in black.

• Bottles of 100. NDC 0603-2553-21

Store and Dispense
At 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]; in a tight, light-resistant container as defined in the USP.

Keep out of reach of children.

Manufactured for:
QUALITEST PHARMACEUTICALS
Huntsville, AL 35811

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