

**LACHMAN CONSULTANT SERVICES, INC.**  
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE, WESTBURY, NY 11590  
(516) 222-6222 • FAX (516) 683-1887

December 22, 2004

**OVERNIGHT COURIER 12/22/04**

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**CITIZEN PETITION**

The undersigned, on behalf of a client, submits this petition in quadruplicate under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("the FDC Act"), 21 U.S.C. § 355(j)(2)(C), and 21 C.F.R. §§ 10.20, 10.30, and 314.93 to request that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application (ANDA) may be submitted for Acetaminophen, Butalbital, Caffeine and Codeine Phosphate Capsules, 300 mg / 50 mg / 40 mg / 30 mg.

**A. Action Requested**

The petitioner requests that the Commissioner of Food and Drugs make a determination that Acetaminophen, Butalbital, Caffeine and Codeine Phosphate Capsules, 300 mg / 50 mg / 40 mg / 30 mg combination drug product is suitable for submission as an ANDA. The reference-listed drug product upon which this petition is based is Fioricet® with Codeine (Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules, 325 mg / 50 mg / 40 mg / 30 mg, Application 20-232), manufactured by Watson Pharmaceuticals. Therefore, this petition requests a change in the strength of one of the active ingredients (acetaminophen) from 325 mg to 300 mg per capsule.

**B. Statement of Grounds**

Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act provides for the submission of an ANDA for a new drug that differs in strength from a listed drug, provided that the FDA has approved a petition seeking permission to file such an application. This petition requests a change in the strength of one of the active ingredients, acetaminophen, from 325 mg per capsule, to 300 mg per capsule. The listing of reference drug product upon which this petition is based, Fioricet® with Codeine Capsules (Acetaminophen, Butalbital, Caffeine and Codeine Phosphate, 325 mg / 50 mg / 40 mg / 30 mg) appears on page 3-2 of the 24<sup>th</sup> Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as "The Orange Book"). See Attachment A.

2004P-0560

CP1

According to the approved labeling of the reference-listed drug product, the usual dosage of Fioricet® with Codeine Capsules is "one or two capsules every four to six hours as needed for pain". The approved package insert for Fioricet® with Codeine Capsules is included in Attachment B. The dosage for the proposed product is "one or two capsules every four to six hours as needed for pain". This dosage is consistent with that stated in the approved labeling of the reference-listed drug product. Also, acetaminophen 300 mg has been approved by the FDA as a safe and effective dose of that component in other combination products, such as Acetaminophen and Codeine Phosphate. Additionally on December 20, 2001, the FDA approved a citizen petition, Docket No. 2001P-0441/CP1, for Hydrocodone Bitartrate and Acetaminophen Tablets, USP 10 mg / 300 mg and more recently on November 23, 2004 the FDA approved a petition, Docket No. 2003P-0414/CP1, approving the same combination, but in a 5 mg / 300 mg strength, confirming that the requested change from a dose of acetaminophen of 325 mg to 300 mg did not raise questions of safety or effectiveness.

In summary, the strength change proposed for the non-narcotic component (a change in the acetaminophen from 325 mg to 300 mg) from that of the reference-listed drug is consistent with, and provides for a product with a safe and effective dose of each of the proposed components, which have been previously approved by the FDA in other combination drug products. The proposed change in strength, therefore, should not raise questions of safety or efficacy of the proposed product. The indication and use remain unchanged, and the proposed dosing is consistent with dosing recommendations in the labeling of the approved reference-listed drug product and the dosing for the non-narcotic component for other FDA approved products containing these ingredients. Therefore, the Agency should conclude that clinical investigations are not necessary to support the proposed change in strength.

The proposed labeling for Acetaminophen, Butalbital, Caffeine and Codeine Phosphate Capsules, 300 mg / 50 mg / 40 mg / 30 mg is included as Attachment C. Labeling for the proposed product will be consistent with the labeling for the approved reference-listed drug product.

For the aforementioned reasons, the undersigned requests that the Commissioner grant this petition and authorize submission of an ANDA for Acetaminophen, Butalbital, Caffeine and Codeine Phosphate Capsules, 300 mg / 50 mg / 40 mg / 30 mg.

**C. Environmental Impact**

According to 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

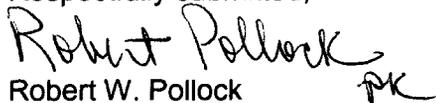
**D. Economic Impact Statement**

According to 21 C.F.R. § 10.30(b), petitioner will, upon request by the Commissioner, submit economic impact information.

**E. Certification**

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,



Robert W. Pollock  
Vice President  
Lachman Consultant Services, Inc.  
1600 Stewart Avenue  
Westbury, NY 11590

RWP/pk

**Attachments:**

- Attachment A: Page 3-2 of the 24<sup>th</sup> Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations
- Attachment B: Approved package insert for Fioricet® with Codeine Capsules
- Attachment C: Proposed labeling for Acetaminophen, Butalbital, Caffeine and Codeine Phosphate Capsules, 300 mg / 50 mg / 40 mg / 30 mg

cc: Emily Thakur (Office of Generic Drugs)

A46P4357d

**LACHMAN CONSULTANT SERVICES, INC.**  
Westbury, NY 11590

# **ATTACHMENT A**

PRESCRIPTION DRUG PRODUCT LIST

3-2

ACETAMINOPHEN; BUTALBITAL

TABLET; ORAL  
SEDAPAP  
 AB + MAYRAND 650MG;50MG N88944 001  
 OCT 17, 1985

ACETAMINOPHEN; BUTALBITAL; CAFFEINE

CAPSULE; ORAL  
ACETAMINOPHEN, BUTALBITAL, AND CAFFEINE  
 AB + MIKART 325MG;50MG;40MG N89007 001  
 MAR 17, 1986

AB BUTALBITAL, ACETAMINOPHEN AND CAFFEINE  
 WEST WARD 500MG;50MG;40MG N40261 001  
 OCT 28, 1998

AB ESGIC-PLUS  
 + MIKART 500MG;50MG;40MG N40085 001  
 MAR 28, 1996

SOLUTION; ORAL  
 ACETAMINOPHEN AND BUTALBITAL AND CAFFEINE  
 + MIKART 325MG/15ML;50MG/15ML;  
 40MG/15ML N40387 001  
 JAN 31, 2003

TABLET; ORAL  
BUTALBITAL, ACETAMINOPHEN AND CAFFEINE  
 AB ABLE 325MG;50MG;40MG N40390 001  
 JUL 23, 2001  
 AB 500MG;50MG;40MG N40394 001  
 JUL 23, 2001  
 AB MALLINCKRODT 325MG;50MG;40MG N87804 001  
 JAN 24, 1985  
 AB MIKART 325MG;50MG;40MG N89175 001  
 JAN 21, 1987  
 + 750MG;50MG;40MG N40496 001  
 DEC 23, 2003  
 AB VINTAGE PHARMS 325MG;50MG;40MG N40511 001  
 AUG 27, 2003  
 AB 500MG;50MG;40MG N40513 001  
 AUG 25, 2003  
 AB WATSON LABS 500MG;50MG;40MG N40267 001  
 JUL 30, 1998  
 AB WEST WARD 325MG;50MG;40MG N89718 001  
 JUN 12, 1995  
 AB BUTALBITAL, ACETAMINOPHEN, AND CAFFEINE  
 WEST WARD 500MG;50MG;40MG N40336 001  
 AUG 18, 1999

ACETAMINOPHEN; BUTALBITAL; CAFFEINE

TABLET; ORAL  
BUTALBITAL, APAP, AND CAFFEINE  
 AB AXIOM PHARM 325MG;50MG;40MG N89536 001  
 FEB 16, 1988

AB ESGIC-PLUS  
 + MIKART 500MG;50MG;40MG N89451 001  
 MAY 23, 1988

AB FIORICET  
 + WATSON PHARMS 325MG;50MG;40MG N88616 001  
 NOV 09, 1984

ACETAMINOPHEN; BUTALBITAL; CAFFEINE; CODEINE PHOSPHATE

CAPSULE; ORAL  
ACETAMINOPHEN, BUTALBITAL, CAFFEINE, AND CODEINE PHOSPHATE  
 AB VINTAGE PHARMS 325MG;50MG;40MG;30MG N75929 001  
 APR 22, 2002

AB BUTALBITAL; ACETAMINOPHEN; AND CAFFEINE WITH CODEINE  
PHOSPHATE  
 WEST WARD 325MG;50MG;40MG;30MG N75618 001  
 MAR 23, 2001

AB BUTALBITAL; ACETAMINOPHEN; CAFFEINE AND CODEINE PHOSPHATE  
 ABLE 325MG;50MG;40MG;30MG N76528 001  
 AUG 21, 2003

AB FIORICET W/ CODEINE  
 + WATSON PHARMS 325MG;50MG;40MG;30MG N20232 001  
 JUL 30, 1992

AB PHRENILIN WITH CAFFEINE AND CODEINE  
 AMARIN PHARMS 325MG;50MG;40MG;30MG N74911 001  
 AUG 22, 2001

ACETAMINOPHEN; CAFFEINE; DIHYDROCODEINE BITARTRATE

CAPSULE; ORAL  
 ACETAMINOPHEN, CAFFEINE, AND DIHYDROCODEINE BITARTRATE  
 + MIKART 356.4MG;30MG;16MG N40109 001  
 AUG 26, 1997

TABLET; ORAL  
 ACETAMINOPHEN, CAFFEINE, AND DIHYDROCODEINE BITARTRATE  
 + MIKART 712.8MG;60MG;32MG N40316 001  
 APR 28, 1999

**ATTACHMENT B**

**Fioricet® with Codeine** 

*(butalbital, acetaminophen, caffeine, and codeine phosphate)*

Capsules

**Rx only**

**DESCRIPTION**

Fioricet® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is supplied in capsule form for oral administration.

Each capsule contains:

- codeine phosphate, USP ..... 30 mg
- butalbital, USP ..... 50 mg
- caffeine, USP ..... 40 mg
- acetaminophen, USP ..... 325 mg

Codeine phosphate [morphine-3-methyl ether phosphate (1:1) (salt) hemihydrate, C<sub>18</sub>H<sub>24</sub>NO<sub>7</sub>P, anhydrous mw 397.37], is a narcotic analgesic and antitussive.

Butalbital (5-allyl-5-isobutylbarbituric acid, C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>, mw 224.26), is a short- to intermediate-acting barbiturate.

Caffeine (1,3,7-trimethylxanthine, C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>, mw 194.19), is a central nervous system stimulant.

Acetaminophen (4'-hydroxyacetanilide, C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>, mw 151.16), is a non-opiate, non-salicylate analgesic and antipyretic.

*Active Ingredients:* codeine phosphate, USP, butalbital, USP, caffeine, USP, and acetaminophen, USP.

*Inactive Ingredients:* black iron oxide, colloidal silicon dioxide, D&C Red #7 (calcium lake), D&C Red #33, FD&C Blue #1, FD&C Blue #1 (aluminum lake), gelatin, magnesium stearate, pregelatinized starch, red iron oxide, sodium lauryl sulfate, and titanium dioxide.

*May also include:* benzyl alcohol, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

**CLINICAL PHARMACOLOGY**

Fioricet® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is a combination drug product intended as a treatment for tension headache.

Fioricet® consists of a fixed combination of butalbital 50 mg, acetaminophen 325 mg and caffeine 40 mg. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

**Pharmacokinetics**

The behavior of the individual components is described below.

**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 crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

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.

See *OVERDOSAGE* for toxicity information.

### ***Butalbital***

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most tissues in the body. Barbiturates in general may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59%-88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-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% is conjugated.

The *in vitro* plasma protein binding of butalbital is 45% over the concentration range of 0.5-20 µg/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.

See *OVERDOSAGE* for toxicity information.

### ***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 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 is recovered in the urine, only 3% is unchanged drug.

See *OVERDOSAGE* for toxicity information.

### ***Acetaminophen***

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25-3 hours, but may be increased by liver damage and

following overdose. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See *OVERDOSAGE* for toxicity information.

## **INDICATIONS**

Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because codeine and butalbital are habit-forming and potentially abusable.

## **CONTRAINDICATIONS**

Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is contraindicated under the following conditions:

- Hypersensitivity or intolerance to acetaminophen, caffeine, butalbital, or codeine.
- Patients with porphyria.

## **WARNINGS**

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is not recommended.

## **PRECAUTIONS**

### **General**

Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) should be prescribed with caution in certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

### **Information for Patients**

Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate).

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate), and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

For information on use in geriatric patients, see PRECAUTIONS, Geriatric Use.

### **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.

Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) 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**

#### ***Codeine***

Codeine may increase serum amylase levels.

#### ***Acetaminophen***

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

### **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 Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate). It is also not known whether Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) 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**

Caffeine, barbiturates, acetaminophen and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate), 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.

### **Geriatric Use**

Clinical studies of Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) 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 overdosage of butalbital.

**Autonomic Nervous:** dry mouth, hyperhidrosis.

**Gastrointestinal:** difficulty swallowing, heartburn, flatulence, constipation.

**Cardiovascular:** tachycardia.

**Musculoskeletal:** leg pain, muscle fatigue.

**Genitourinary:** diuresis.

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

**The following adverse reactions have been voluntarily reported as temporally associated with 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 Fioricet® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate). 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 Fioricet® (Butalbital, Acetaminophen, and Caffeine Tablets, USP).

## **DRUG ABUSE AND DEPENDENCE**

### **Controlled Substance**

Fioricet® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is controlled by the Drug Enforcement Administration and is classified under Schedule III.

### **Abuse and Dependence**

#### **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.

#### **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.

## **OVERDOSAGE**

Following an acute overdose of Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate), 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 necroses, hypoglycemic coma, and thrombocytopenia 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 48-72 hours post-ingestion. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams. Acute *caffeine* poisoning may cause insomnia, restlessness, tremor, and delirium, tachycardia, and extrasystoles.

## **Treatment**

A single or multiple overdose with Fioricet<sup>®</sup> with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. The value of vasopressor agents such as Norepinephrine or Phenylephrine Hydrochloride in treating hypotension is questionable since they increase vasoconstriction and decrease blood flow. However, if prolonged support of blood pressure is required, Norepinephrine Bitartrate (Levophed<sup>®</sup>)\* may be given I.V. with the usual precautions and serial blood pressure monitoring. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone 0.4-2 mg is given parenterally. Since the duration of action of codeine may exceed that of the naloxone, the patient should be kept under continuous 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.

If the dose of acetaminophen may have exceeded 140 mg/kg, N-acetyl-cysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels 4 or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

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

#### **Toxic doses (for adults)**

##### ***Butalbital:***

toxic dose 1.0 g  
(20 capsules of Fioricet<sup>®</sup> with Codeine)

##### ***Acetaminophen:***

toxic dose 10 g  
(30 capsules of Fioricet<sup>®</sup> with Codeine)

##### ***Caffeine:***

toxic dose 1.0 g  
(25 capsules of Fioricet<sup>®</sup> with Codeine)

##### ***Codeine:***

toxic dose 240 mg  
(8 capsules of Fioricet<sup>®</sup> with Codeine)

#### **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**

**Fioricet® with Codeine**

**(butalbital, acetaminophen, caffeine, and codeine phosphate) Capsules**

Dark blue, opaque cap with a grey, opaque body. Cap is imprinted twice in light-blue with “FIORICET” and “CODEINE”. Body is imprinted twice with four-head profile “” in red.

Bottle of 100 ..... (NDC 0078-0243-05)

***Store and Dispense***

Below 30°C (86°F); tight container.

\*Levophed is a registered Trademark of Sanofi Winthrop Pharmaceuticals.

Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey 07936

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**ATTACHMENT C**



# Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules

R<sub>x</sub> only

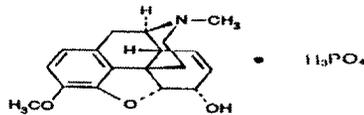
## DESCRIPTION

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate is supplied in capsule form for oral administration.

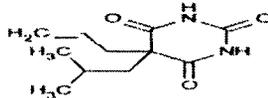
Each capsule contains:

codeine phosphate, USP .....	30 mg
Butalbital, USP .....	50 mg
caffeine, USP .....	40 mg
acetaminophen, USP .....	300 mg

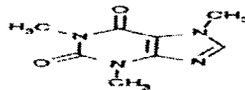
Codeine phosphate [morphine-3-methyl ether phosphate (1:1) (salt) hemihydrate, C<sub>18</sub>H<sub>24</sub>N<sub>0</sub>7P, anhydrous mw 397.37], is a narcotic analgesic and antitussive. The structural formula of codeine phosphate is:



Butalbital (5-allyl-5-isobutylbarbituric acid, C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>, mw 224.26), is a short-to intermediate-acting barbiturate. The structural formula of butalbital is:



Caffeine (1,3,7-trimethylxanthine, C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>, mw 194.19), is a central nervous system stimulant. The structural formula of caffeine is:



Acetaminophen (4'-hydroxyacetanilide, C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>, mw 151.16), is a non-opiate, non-salicylate analgesic and antipyretic. The structural formula of acetaminophen is:



*Active Ingredients:* codeine phosphate, USP, butalbital, USP, caffeine, USP, and acetaminophen, USP.

*Inactive Ingredients:* This information will be provided upon submission of the ANDA.

## CLINICAL PHARMACOLOGY

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate is a combination drug product intended as a treatment for tension headache.

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate consists of a fixed combination of butalbital 50 mg, acetaminophen 300 mg, caffeine 40 mg and codeine phosphate 30 mg. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

### **Pharmacokinetics**

The behavior of the individual components is described below.

#### **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 crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

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.

See *OVERDOSAGE for toxicity* information.

#### **Butalbital**

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most tissues in the body. Barbiturates in general may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59% to 88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-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% is 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% to 45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood cells.

See *OVERDOSAGE for toxicity* information.

#### **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 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 is recovered in the urine, only 3% is unchanged drug.

See *OVERDOSAGE for toxicity* information.

#### **Acetaminophen**

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of

acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See *OVERDOSAGE* for toxicity information.

### **INDICATIONS AND USAGE**

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate capsule is indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

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

### **CONTRAINDICATIONS**

This combination product is contraindicated under the following conditions:

- Hypersensitivity or intolerance to acetaminophen, caffeine, butalbital, or codeine.
- Patients with porphyria.

### **WARNINGS**

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of this combination product is not recommended.

### **PRECAUTIONS**

#### **General**

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate should be prescribed with caution in certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

#### **Information for Patients**

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this combination product.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with this combination product and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

For information on use in geriatric patients, refer to *PRECAUTIONS/Geriatric Use*.

**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 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****Codeine**

Codeine may increase serum amylase levels.

**Acetaminophen**

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

**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. It is also not known whether this combination product can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This combination product 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**

Caffeine, barbiturates, acetaminophen and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from this combination product, 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.

**Geriatric Use**

Clinical studies of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate 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 overdosage of butalbital.

**Autonomic Nervous:** dry mouth, hyperhidrosis.

**Gastrointestinal:** difficulty swallowing, heartburn, flatulence, constipation.

**Cardiovascular:** tachycardia.

**Musculoskeletal:** leg pain, muscle fatigue.

**Genitourinary:** diuresis.

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

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

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

**Autonomic Nervous:** epistaxis, flushing, miosis, salivation.

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

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

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

**Urinary:** kidney impairment, urinary difficulty.

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

The following adverse drug events may be borne in mind as potential effects of the components of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate . 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 Fioricet® (Butalbital, Acetaminophen, and Caffeine Tablets, USP).

## **DRUG ABUSE AND DEPENDENCE**

### **Controlled Substance**

Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate is controlled by the Drug Enforcement Administration and is classified under Schedule III.

### **Abuse and Dependence**

#### **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.

#### **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.

## **OVERDOSAGE**

Following an acute overdosage of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate , 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** includes drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock. Toxicity from **codeine poisoning** includes the opioid triad of: pinpoint pupils, depression of respiration, and loss of consciousness. Convulsions may occur. In **acetaminophen overdosage:** dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necroses, hypoglycemic coma, and thrombocytopenia 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. In adults hepatic toxicity has rarely been reported with acute overdoses of less than

10 grams, or fatalities with less than 15 grams. **Acute caffeine poisoning** may cause insomnia, restlessness, tremor, and delirium, tachycardia, and extrasystoles.

### **Treatment**

A single or multiple overdose with this combination product is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. The value of vasopressor agents such as Norepinephrine or Phenylephrine Hydrochloride in treating hypotension is questionable since they increase vasoconstriction and decrease blood flow. However, if prolonged support of blood pressure is required, Norepinephrine Bitartrate (Levophed®)\* may be given I.V. with the usual precautions and serial blood pressure monitoring. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone 0.4 to 2 mg is given parenterally. Since the duration of action of codeine may exceed that of the naloxone, the patient should be kept under continuous 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.

If the dose of acetaminophen may have exceeded 140 mg/kg, N-acetyl-cysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels 4 or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

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

### **Toxic doses (for adults)**

#### **Butalbital:**

toxic dose 1 g  
(20 capsules of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate)

#### **Acetaminophen:**

toxic dose 10 g  
(30 capsules of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate)

#### **Caffeine:**

toxic dose 1 g  
(25 capsules of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate)

#### **Codeine:**

toxic dose 240 mg  
(8 capsules of Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate)

### **DOSAGE AND ADMINISTRATION**

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

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

## **HOW SUPPLIED**

### **Butalbital, Acetaminophen, Caffeine, and Codeine Phosphate Capsules**

<Color> opaque cap with a <Color> opaque body, and body is imprinted with <Code> in black ink.

Bottle of 100 (NDC XXXXX-XXX-XX)

Bottle of 500 (NDC XXXXX-XXX-XX)

### ***Store and Dispense***

Store at 20 to 25°C (68 to 77°F) in a tight, light-resistant container.

\*Fiorinal® with Codeine is a registered trademark of Novartis Pharmaceuticals.

\*Fioricet® is a registered trademark of Novartis Pharmaceuticals.

\*Levophed® is a registered Trademark of Sanofi Winthrop Pharmaceuticals.

Manufactured by:  
<Place manufacturer and address here>

(Rev. 12/04)