LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 5

Fioricet With Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) Capsule [Watson Pharma, Inc.]

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, $C_{18}H_{24}NO_7P$, anhydrous mw 397.37], is a narcotic analgesic and antitussive.

Butalbital (5-allyl-5-isobutylbarbituric acid, $C_{11}H_{16}N_2O_3$, mw 224.26), is a short- to intermediate-acting barbiturate.

Caffeine (1,3,7-trimethylxanthine, $C_8H_{10}N_4O_2$, mw 194.19), is a central nervous system stimulant.

Acetaminophen (4′-hydroxyacetanilide, $C_8H_9NO_2$, 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 (about 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 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.

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 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

Fioricet® 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® 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® 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® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) is not recommended.

PRECAUTIONS

General

Fioricet® 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® 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® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate).

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with Fioricet® 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® 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® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate). It is also not known whether Fioricet® with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fioricet® 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® 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® 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 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.

OVERDOSAGE

Following an acute overdosage of Fioricet® 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*** 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 48-72 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® 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®)* 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® with Codeine)
Acetaminophen:	
toxic dose 10 g	(30 capsules of Fioricet® with Codeine)
Caffeine:	
toxic dose 1.0 g	(25 capsules of Fioricet® with Codeine)
Codeine:	
toxic dose 240 mg	(8 capsules of Fioricet® 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 light 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 52544-958-01)

Store and Dispense
Below 30°C (86°F); tight container.

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Watson Pharma, Inc.
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Fioricet with Codeine (butalbital, acetaminophen, caffeine, and codeine phosphate)

PRODUCT INFO

Product Code	52544-958	**Dosage Form**	CAPSULE
Route Of Administration	ORAL	**DEA Schedule**	CIII

INGREDIENTS

Name (Active Moiety)	Type	Strength
codeine phosphate (codeine)	Active	30 MILLIGRAM In 1 CAPSULE
butalbital (butalbital)	Active	50 MILLIGRAM In 1 CAPSULE
caffeine (caffeine)	Active	40 MILLIGRAM In 1 CAPSULE
acetaminophen (acetaminophen)	Active	325 MILLIGRAM In 1 CAPSULE
black iron oxide	Inactive	
colloidal silicon dioxide	Inactive	
D&C Red #7 (calcium lake)	Inactive	
D&C Red #33	Inactive	
FD&C Blue #1	Inactive	
FD&C Blue #1 (aluminum lake)	Inactive	
gelatin	Inactive	
magnesium stearate	Inactive	
pregelatinized starch	Inactive	
red iron oxide	Inactive	
sodium lauryl sulfate	Inactive	
titanium dioxide	Inactive	
benzyl alcohol butylparaben	Inactive	
carboxymethylcellulose sodium	Inactive	
edetate calcium disodium	Inactive	
methylparaben	Inactive	
propylparaben	Inactive	
silicon dioxide	Inactive	
sodium propionate	Inactive	

IMPRINT INFORMATION

Characteristic	Appearance	Characteristic	Appearance
Color	BLUE (DARK BLUE, OPAQUE) , GRAY (LIGHT GRAY, OPAQUE)	**Score**	1

Shape	CAPSULE	**Symbol**	true
Imprint Code	FIORICET;CODEINE	**Coating**	false
Size	22mm		

PACKAGING

#	NDC	Package Description	Multilevel Packaging
1	52544-958-01	100 CAPSULE In 1 BOTTLE	None

Revised: 10/2006