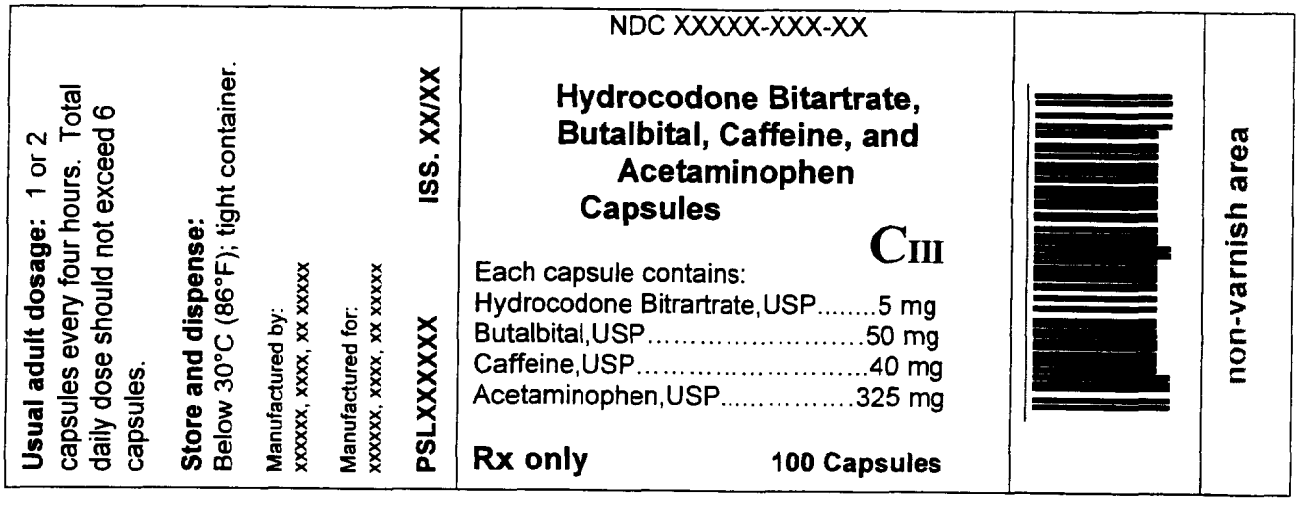
ATTACHMENT 6

DRAFT GENERIC LABELING

Distributor NDC # to be printed here



Manufacturer and Distributor Name and their locations to be printed here along with the actual PSL # and ISS date

Lot #:
Expiration Date:
(To be printed here)

Hydrocodone Bitartrate, Butalbital, Caffeine, and Acetaminophen

Capsules **CIII**

Rx only

DESCRIPTION

The hydrocodone bitartrate, butalbital, caffeine, and acetaminophen product is supplied in capsule form for oral administration.

Each capsule contains:

hydrocodone bitartrate, USP	5 mg
butalbital, USP	50 mg
caffeine, USP	40 mg
acetaminophen, USP	325 mg

Hydrocodone bitartrate [$C_{18}H_{21}NO_3C_4H_6O_6$ 494.49, Morphinan-6-one, 4, 5α-epoxy-3-methoxy-17-methy 1-, (5), [R-(R*, R*)]-2, 3-dihydroxybutanedioate (1:1), hydrate (2:5) 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: hydrocodone bitartrate, USP, butalbital, USP, caffeine, USP, and acetaminophen, USP.

Inactive Ingredients: FD&C Blue #1, gelatin, magnesium stearate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood and mental clouding.

Pharmacokinetics

The behavior of the individual components is described below.

Hydrocodone

Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

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 ∝g/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

Hydrocodone bitartrate, butalbital, caffeine, and acetaminophen is indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of hydrocodone bitartrate, butalbital, caffeine, and acetaminophen 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

Hydrocodone bitartrate, butalbital, caffeine, and acetaminophen are contraindicated under the following conditions:
– Hypersensitivity or intolerance to acetaminophen, caffeine, butalbital, or hydrocodone.
– 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.

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

Butalbital and hydrocodone are both habit-forming and potentially abusable. Consequently, the extended use of the hydrocodone bitartrate, butalbital, caffeine, and acetaminophen product is not recommended.

PRECAUTIONS

General

Hydrocodone bitartrate, butalbital, caffeine, and acetaminophen 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

Hydrocodone bitartrate, butalbital, caffeine, and acetaminophen 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 the hydrocodone bitartrate, butalbital, caffeine, and acetaminophen product.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with Hydrocodone bitartrate, butalbital, caffeine, and acetaminophen and should be avoided.

Hydrocodone 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.

Hydrocodone bitartrate, butalbital, caffeine, and acetaminophen 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

Hydrocodone

Hydrocodone 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, hydrocodone 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 this product. It is also not known whether this product can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This 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 hydrocodone during labor may lead to respiratory depression in the neonate.

Nursing Mothers

Caffeine, barbiturates, acetaminophen and hydrocodone 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 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

Safety and effectiveness in geriatric patients have not been established.

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 Hydrocodone bitartrate, butalbital, caffeine, and acetaminophen. 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.

Hydrocodone: 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

This product is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Abuse and Dependence

Hydrocodone

Hydrocodone 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 this product, toxicity may result from the barbiturate, the hydrocodone, 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 **hydrocodone** 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 this 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 0.4-2 mg is given parenterally. Since the duration of action of hydrocodone 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 hydrocodone bitartrate, butalbital, caffeine, and acetaminophen)

Acetaminophen:

toxic dose 10 g
(30 capsules of hydrocodone bitartrate, butalbital, caffeine, and acetaminophen)

Caffeine:

toxic dose 1.0 g
(25 capsules of hydrocodone bitartrate, butalbital, caffeine, and acetaminophen)

Hydrocodone:

toxic dose 40 mg
(8 capsules of hydrocodone bitartrate, butalbital, caffeine, and acetaminophen)

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

Hydrocodone Bitartrate, Butalbital, Caffeine, and Acetaminophen Capsules

Dark blue, opaque cap with a light blue, opaque body. Cap is imprinted with "XXXXX". Body is imprinted with "325".

Bottle of 100 ..... (XXX XXXX-XXXX-XX)

Store and Dispense

Below 30°C (86°F); tight container.

*Levophed is a registered Trademark of Sanofi Winthrop Pharmaceuticals.

**Fiorinal is a registered Trademark of Novartis Pharmaceuticals.

Manufactured for:
XXXXXXXXX
XXXXXXXXXX

Manufactured by:
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