

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 and Caffeine Capsules USP, 300 mg / 50 mg / 40 mg.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs make a determination that Acetaminophen, Butalbital and Caffeine Capsules USP, 300 mg / 50 mg / 40 mg combination drug product is suitable for submission as an ANDA. The reference-listed drug product upon which this petition is based is Acetaminophen, Butalbital and Caffeine Capsules USP, 325 mg / 50 mg / 40 mg, Application 89-007, manufactured by Mikart. 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, Acetaminophen, Butalbital and Caffeine Capsules USP, 325 mg / 50 mg / 40 mg appears on page 3-2 of the 24th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as "The Orange Book"). See Attachment A.

2004P-0561

CP1

According to the approved labeling of the reference-listed drug product, the usual dosage of Acetaminophen, Butalbital and Caffeine Capsules USP, 325 mg / 50 mg / 40 mg is "one or two capsules every four to six hours as needed for pain". The approved package insert for Acetaminophen, Butalbital and Caffeine Capsules USP, 325 mg / 50 mg / 40 mg, 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 and Caffeine Capsules USP, 300 mg / 50 mg / 40 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 and Caffeine Capsules USP, 300 mg / 50 mg / 40 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.

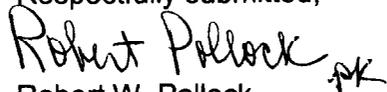
D. Economic Impact Statement

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 24th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations
- Attachment B: Approved package insert for Acetaminophen, Butalbital and Caffeine Capsules USP, 325 mg / 50 mg / 40 mg
- Attachment C: Proposed labeling for Acetaminophen, Butalbital and Caffeine Capsules USP, 300 mg / 50 mg / 40 mg

cc: Emily Thakur (Office of Generic Drugs)

A46P4357

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

BUTALBITAL, ACETAMINOPHEN AND CAFFEINE

AB WEST WARD 500MG;50MG;40MG N40261 001
OCT 28, 1998

ESGIC-PLUS

AB + 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

BUTALBITAL, ACETAMINOPHEN, AND CAFFEINE

AB 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

ESGIC-PLUS

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

FIORICET

AB + 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

BUTALBITAL; ACETAMINOPHEN; AND CAFFEINE WITH CODEINE PHOSPHATE

AB WEST WARD 325MG;50MG;40MG;30MG N75618 001
MAR 23, 2001

BUTALBITAL; ACETAMINOPHEN; CAFFEINE AND CODEINE PHOSPHATE

AB ABLE 325MG;50MG;40MG;30MG N76528 001
AUG 21, 2003

FIORICET W/ CODEINE

AB + WATSON PHARMS 325MG;50MG;40MG;30MG N20232 001
JUL 30, 1992

PHRENILIN WITH CAFFEINE AND CODEINE

AB 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

BUTALBITAL, ACETAMINOPHEN AND CAFFEINE TABLETS USP
50 mg/325 mg/40 mg
Rx only

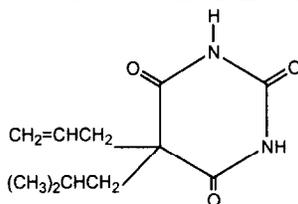
Code 687Z00

Rev. 08/02

DESCRIPTION:

Butalbital, acetaminophen and caffeine are supplied in tablet form for oral administration.

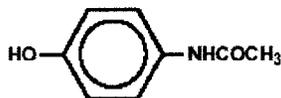
Butalbital (5-allyl-5-isobutylbarbituric acid), a slightly bitter, white, odorless, crystalline powder, is a short to intermediate acting barbiturate. It has the following structural formula:



$C_{11}H_{16}N_2O_3$

MW = 224.26

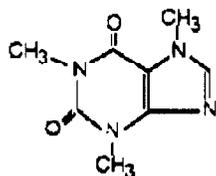
Acetaminophen (4'-hydroxyacetanilide), a slightly bitter, white, odorless, crystalline powder, is a non-opiate, nonsalicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$

MW = 151.16

Caffeine (1,3,7-trimethylxanthine), a bitter, white powder or white-glistening needles, is a central nervous system stimulant. It has the following structural formula:



$C_8H_{10}N_4O_2$

MW = 194.19

Each tablet contains:

Butalbital 50 mg

Warning: May be habit forming.

Acetaminophen 325 mg

Caffeine 40 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized corn starch and stearic acid.

CLINICAL PHARMACOLOGY:

This combination drug product is intended as a treatment for tension headache.

It consists of a fixed combination of butalbital, acetaminophen and caffeine. 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.

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 (20-45%) 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.)

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 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.)

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.)

INDICATIONS AND USAGE:

Butalbital, acetaminophen and caffeine tablets are indicated for the relief of the symptom

complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

CONTRAINDICATIONS:

This product is contraindicated under the following conditions:

- Hypersensitivity or intolerance to any component of this product.
- Patients with porphyria.

WARNINGS:

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

PRECAUTIONS:

General: Butalbital, acetaminophen and caffeine tablets 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, or acute abdominal conditions.

Information for Patients: This product 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 product.

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

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.

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 and caffeine may enhance the effects of: other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions: Acetaminophen 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 or butalbital have a potential for carcinogenesis, mutagenesis or impairment of fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with this combination product. It is also not known whether butalbital, acetaminophen and caffeine 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 two 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.

Nursing Mothers: Caffeine, barbiturates and acetaminophen 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 butalbital, acetaminophen and caffeine, 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 below the age of 12 have not been established.

Geriatric Use: Clinical studies of butalbital, acetaminophen and caffeine tablets 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 System: 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 System: 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.

Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported.

The following adverse drug events may be borne in mind as potential effects of the components of this product. 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.

DRUG ABUSE AND DEPENDENCE:

Abuse and Dependence:

Butalbital: *Barbiturates may be habit-forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1500 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 butalbital, acetaminophen and caffeine, toxicity may result from the barbiturate or the acetaminophen. Toxicity due to 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.

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, 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. Pressors should be avoided. 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.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four 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 tablets)

Acetaminophen: toxic dose

10 g (30 tablets)

Caffeine: toxic dose

1 g (25 tablets)

DOSAGE AND ADMINISTRATION:

One or two tablets every four hours. Total daily dosage should not exceed 6 tablets. Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED:

Butalbital, Acetaminophen and Caffeine Tablets USP contain butalbital 50 mg (**Warning: May be habit-forming**), acetaminophen 325 mg and caffeine 40 mg. Tablets are white, capsule shaped, single-scored with the logo "MIA/110", and are supplied in bottles of 100 and bottles of 500.

Storage: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F) (see USP).

Dispense in a tight, light-resistant container with a child-resistant closure.

Rx only

Manufactured by:
MIKART, INC.
Atlanta, GA 30318

Rev. 08/02

Code 687Z00

ATTACHMENT C

Butalbital, Acetaminophen, and Caffeine Capsules

R_x only

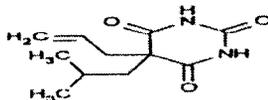
DESCRIPTION

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

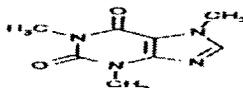
Each capsule contains:

Butalbital, USP	50 mg
caffeine, USP	40 mg
acetaminophen, USP	300 mg

Butalbital (5-allyl-5-isobutylbarbituric acid, C₁₁H₁₆N₂O₃, mw 224.26), is a short-to intermediate-acting barbiturate. The structural formula of butalbital is:



Caffeine (1,3,7-trimethylxanthine, C₈H₁₀N₄O₂, mw 194.19), is a central nervous system stimulant. The structural formula of caffeine is:



Acetaminophen (4'-hydroxyacetanilide, C₈H₉NO₂, mw 151.16), is a non-opiate, non-salicylate analgesic and antipyretic. The structural formula of acetaminophen is:



Active Ingredients: butalbital, USP, caffeine, USP, and acetaminophen, USP.

Inactive Ingredients: This information will be provided when the ANDA is submitted.

CLINICAL PHARMACOLOGY

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

Butalbital, Acetaminophen, and Caffeine consists of a fixed combination of butalbital 50 mg, acetaminophen 300 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.

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, and Caffeine 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, and Caffeine in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

CONTRAINDICATIONS

This combination product is contraindicated under the following conditions:

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

WARNINGS

In the presence of head injury or other intracranial lesions, the respiratory depressant effects butalbital 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.

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

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

PRECAUTIONS

General

Butalbital, Acetaminophen, and Caffeine 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, and Caffeine 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.

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, and Caffeine may enhance the effects of:

- Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions

Acetaminophen

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

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, and Caffeine. 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, and acetaminophen 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, and Caffeine 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® , a related product containing aspirin, butalbital, and caffeine.

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, and Caffeine. 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.

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, and Caffeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Abuse and Dependence

Butalbital

Barbiturates may be habit-forming: Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than 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, and Caffeine, 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. 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.

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 Anacet with Codeine)

Acetaminophen:

toxic dose 10 g
(30 capsules of Anacet with Codeine)

Caffeine:

toxic dose 1 g
(25 capsules of Anacet 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 combination product is not recommended because of the potential for physical dependence.

HOW SUPPLIED**Butalbital, Acetaminophen, and Caffeine 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)