

January 30, 2002

SUITABILITY PETITION

Dockets Management Branch
Food and Drug Administration (HFA-305)
12420 Parklawn Drive (Room 1-23)
Rockville, MD 20857

RE: Suitability Petition

Dear Sir/Madam:

Enclosed are four copies of a suitability petition we are filing on behalf of Atley Pharmaceuticals, Inc., Ashland, VA 23005. The petition requests the Commissioner to permit Atley to file an abbreviated new drug application (ANDA) for a tableted product containing butalbital and acetaminophen at strengths different from the RLD drugs as defined in the attached petition.

Sincerely,



Paul W. Carr, P.E., R.A.C.
Regulatory Consultant

Attachment

cc: Atley Pharmaceuticals, Inc.

PWC:pbh

02P.0056

CP1

SUITABILITY PETITION

Petition Filed By:

**Atley Pharmaceuticals, Inc. (Atley)
14433 N. Washington Highway
Ashland, VA 23005**

Proposed Products:

**Oral Tablet Dosage Forms Containing
25 mg butalbital/300 mg acetaminophen
50 mg butalbital/600 mg acetaminophen**

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SUITABILITY PETITION

The undersigned submits this Suitability Petition under Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 355(j)(2)(C)), which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR §5.10. Petitioner requests the Commissioner of Food and Drugs to make a determination that the drug products hereinafter described are suitable for consideration under an abbreviated new drug application (ANDA).

A. Action Requested

ATLEY requests a determination that a drug product containing 300 mg acetaminophen, 25 mg butalbital and a drug product containing 600 mg acetaminophen, 50 mg butalbital in tablet form for oral administration is suitable for evaluation under an ANDA.

We also request the Food and Drug Commissioner to grant a waiver from the requirements of a pediatric study for a change in dosage form on the basis that this combination of active ingredients is currently approved by the Food and Drug Administration at other strength combinations, all for the same disease conditions, but allows the physician to properly prescribe the appropriate strength depending on the severity of the condition. We understand the agency's desire to seek information regarding the use of this drug in various pediatric populations. However, in this case the product labeling already includes approved uses and dosing instructions for the most significant patient population. We propose that the concept of a standardized dosage adjustment for safety or efficacy, which is the usual goal of pediatric studies, is not relevant to this drug. In accordance with 21 CFR 314.55(c) the Commissioner may grant full or partial waiver of the study requirements on his own initiative or at the request of the applicant.

B. Statement of Grounds

The FDCA allows an ANDA applicant to petition FDA for permission to file an ANDA for a drug product whose strength differs from that of the listed drug. See 21 U.S.C. §355(j)(2)(C); 57 Fed. Reg. 17950-17952(1992).

In the case of the proposed products there are reference listed drug (RLD) products for tablets published in, "Approved Drug Products with Therapeutic Equivalence Evaluations," (The Orange Book) covering strengths of acetaminophen from 325 mg to 650 mg along with a butalbital strength of 50 mg (Attachment 1). We have also attached a table listing products similar to the proposed products that have been approved or for which suitability petitions have been accepted (Attachment 2)

The proposed products are similar to the reference (RLD) products in that the proposed products contain acetaminophen and butalbital in combination as a proven product for the relief of the symptom complex of tension (or muscle contraction) headache.

The legal basis under which this application proceeds is as promulgated in the FDCA, noted above, which allows the Commissioner to accept a generic drug application for a drug which differs in dosage strengths from the pioneer or reference drug product. The petitioner is not aware of any information that would be unfavorable to the granting of the requested action.

C. Environmental Impact

ATLEY hereby requests a categorical exclusion from the requirement of preparing an environmental assessment. As provided in 21 CFR 25.31, neither an environmental assessment nor an environmental impact statement is required. To the best of the petitioner's knowledge, no extraordinary circumstances exist that may significantly affect the human environment as discussed under 21 CFR 25.21.

D. Economic Impact

As provided in 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

E. Identification of RLD

ATLEY is attaching labeling for the RLD product to which they are comparing the proposed drugs. These products are as follows:

Application No.	Name of Drug	Applicant
087811	Phrenilin	Amarin Pharmaceuticals, Inc. (Marketed by Carrick Laboratories, Inc.)

F. Labeling

Attachment 3 provides copies of the proposed generic product labeling and Attachment 4 provides copies of the reference drug labeling. [Please note: Atley is still in the process of finalizing the design of the product container label. Lot No. and Expiration Date will be imprinted on the labels during the labeling operations.]

Following is a description of the differences between the proposed generic product labeling and the RLD package inserts.

PACKAGE INSERT

1. Add "Rx Only" and "CIII" to the beginning of the text
 2. Replace "Phrenilin®" and "Phrenilin Forte®" trade names with the Atley generic names of "Butalbital 25 mg/Acetaminophen 300 mg or Butalbital 50 mg/Acetaminophen 600 mg."
- **Description**
 - A. Replace the trade name Phrenilin with the above noted generic names
 - B. Change the descriptive text as follows:

FROM:

TO THE FOLLOWING:

DESCRIPTION

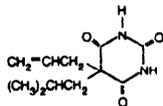
PHRENILIN®: Each PHRENILIN® tablet, for oral administration, contains Butalbital*, USP 50 mg *(WARNING- May be habit forming), Acetaminophen, USP 325 mg.

In addition each PHRENILIN Tablet contains the following inactive ingredients: alginic acid, cornstarch, D&C Red No. 27 - Aluminum Lake, FD&C Blue No. 1-Aluminum Lake, gelatin, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

PHRENILIN® FORTE: Each PHRENILIN® FORTE capsule, for oral administration, contains Butalbital*, USP 50 mg *(WARNING - May be habit forming), Acetaminophen, USP 650 mg.

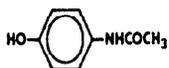
In addition each PHRENILIN FORTE capsule may also contain the following inactive ingredients: benzyl alcohol, butyl-paraben, D&C Red No. 28, D&C Red No. 33, edetate calcium disodium, FD&C Blue No. 1, FD&C Red No. 40, gelatin, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, sodium propionate and titanium dioxide.

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:



C₁₁H₁₆N₂O₃ MW = 224.26

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

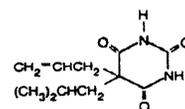


C₈H₉NO₂ MW - 151.16

DESCRIPTION

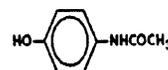
Butalbital 25 mg/Acetaminophen 300 mg [or Butalbital 50 mg/Acetaminophen 600 mg] is supplied in tablet form for oral administration.

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:



C₁₁H₁₆N₂O₃ MW = 224.26

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



C₈H₉NO₂ MW - 151.16

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

Each Butalbital 25 mg/Acetaminophen 300 mg Tablet contains:

Butalbital*, USP.....25 mg
*Warning: May be habit forming
Acetaminophen, USP.....300 mg

Or

Each Butalbital 50 mg/Acetaminophen 600 mg Tablet contains:

Butalbital* USP.....50 mg
*Warning: May be habit forming
Acetaminophen, USP.....600 mg

- **CLINICAL PHARMACOLOGY**

No changes

- **INDICATIONS AND USAGE**

Changed "PHRENILIN tablets and PHRENILIN FORTE capsules" to the generic names

- **CONTRAINDICATIONS**

No changes

- **WARNINGS**

No changes

- **PRECAUTIONS**

Changed "PHRENILIN tablets and PHRENILIN FORTE capsules" to the generic names in all subsections that these names appeared.

- **ADVERSE REACTIONS**

No changes

- **DRUG ABUSE AND DEPENDENCE**

No changes

- **OVERDOSAGE**

Toxic Doses (for Adults)

Changed:

PHRENILIN tablets (Butalbital 50 mg and Acetaminophen 325 mg tablets)

Butalbital: toxic dose 1 g (20 tablets)

Acetaminophen: toxic dose 10 g (30 tablets)

PHRENILIN FORTE capsules (Butalbital 50 mg and Acetaminophen 650 mg capsules)

Butalbital: toxic dose 1 g (20 capsules)

Acetaminophen: toxic dose 10 g (15 capsules)

To:

[Butalbital 25 mg/Acetaminophen 300 mg tablets]

Butalbital: toxic dose 1 g (40 tablets)

Acetaminophen: toxic dose 10 g (33 tablets)

OR

[Butalbital 50 mg/Acetaminophen 600 mg tablets]

Butalbital: toxic dose 1 g (20 tablets)

Acetaminophen: toxic dose 10 g (16 tablets)

- **DOSAGE AND ADMINISTRATION**

No changes

• **How Supplied**

A. Changed statement from:

TO READ AS FOLLOWS:

HOW SUPPLIED

PHRENILIN®: Pale violet scored tablets with the letter C on one side and 8650 on the other, in bottles of 100 (NDC 0086-0050-10). Each tablet contains butalbital, USP 50 mg

(WARNING: May be habit forming) and acetaminophen, USP 325 mg.

PHRENILIN® FORTE: Amethyst, opaque capsules imprinted with the letter C and 8656, in bottles of 100 (NDC 0086-0056-10). Each capsule contains butalbital, USP 50 mg

(WARNING: May be habit forming) and acetaminophen USP 650 mg.

Store PHRENILIN® and PHRENILIN® FORTE (Butalbital and Acetaminophen) at controlled room temperature, 15°-30°C (59°-86°F). Dispense in a tight container as defined in the USP.

Caution: Federal Law Prohibits Dispensing Without Prescription

The most recent revision of this labeling is June 1993.

Manufactured for Carnrick Laboratories, Inc.

HOW SUPPLIED

Butalbital 25 mg/Acetaminophen 300 mg
Tablets are supplied in bottles of 100 tablets, NDC 59702-253-01, and in bottles of 500, NDC 59702-253-05. Each tablet contains butalbital, USP 25 mg (Warning: May be habit forming) and acetaminophen, USP 300 mg. Tablets are uncoated, white, capsule-shaped and are embossed “___” scored “___” on one side.

Storage: Protect from light and moisture. Store at controlled room temperature, 15°-30°C (59°-86°F).

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

Rx only

Manufactured For:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005

Manufactured By:
PharmaFab
Grand Prairie, TX 75050

PIN

ISS 12/01

Made in USA

OR

Butalbital 50 mg/Acetaminophen 600 mg
Tablets are supplied in bottles of 100 tablets. NDC 59702-506-01, and in bottles of 500 tablets, NDC 59702-506-05. Each tablet contains Butalbital, USP 50 mg (Warning: May be habit forming) and acetaminophen, USP 600 mg. Tablets are uncoated, white, capsule-shaped and are embossed “___” scored “___” on one side.

Storage: Protect from light and moisture. Store at controlled room temperature, 15°-30°C (59°-86°F).

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

Rx only

Manufactured For:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005

Manufactured By:
PharmaFab
Grand Prairie, TX 75050

PIN

ISS 12/01

Made in USA

G. 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 us that are unfavorable to the petition.

Typed Name: Craig L. Attkisson

Signature: 

Title: President

Name of Petitioner: Atley Pharmaceuticals, Inc. (Atley)

Mailing Address: 14433 N. Washington Highway
Ashland, VA 23005

Telephone No: (804) 752-8400

ATT. 1

ATTACHMENT 1
LISTING OF REFERENCE LISTED DRUGS (RLDs)

Appl No			Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
087233	AB	Yes	ACETAMINOPHEN; BUTALBITAL	Tablet; Oral	325MG;50MG	PHRENIEN	ALMAREX PHARMS
068944	AB	Yes	ACETAMINOPHEN; BUTALBITAL	Tablet; Oral	650MG;50MG	SEDAPAP	MAYRAND

ATT. 2

ATTACHMENT 2
LISTING OF SIMILAR PRODUCTS

Appl No	AB	No	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
089987	AB	No	ACETAMINOPHEN; BUTALBITAL	Tablet; Oral	325MG;50MG	BUTAPAP	MIKART
089988	AB	No	ACETAMINOPHEN; BUTALBITAL	Tablet; Oral	650MG;50MG	BUTAPAP	MIKART

ATT. 3

ATTACHMENT 3
DRAFT GENERIC LABELS

Butalbital 25 mg/Acetaminophen 300 mg

Rx Only

CIII

DESCRIPTION

Butalbital 25 mg/Acetaminophen 300 mg is supplied in tablet form for oral administration.

Each Butalbital 25 mg/Acetaminophen 300 mg Tablet contains:

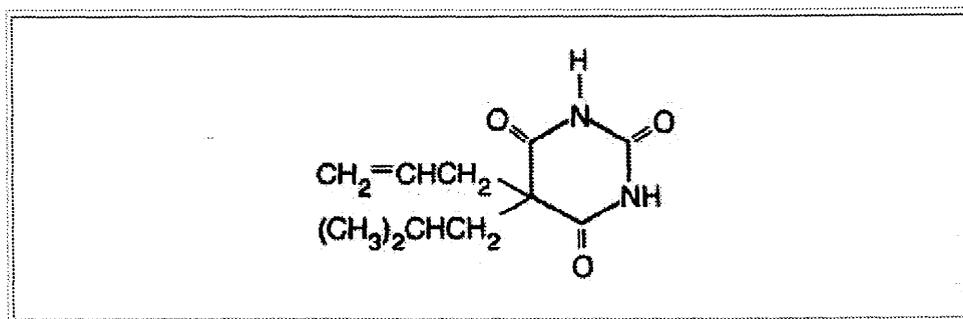
Butalbital*, USP25 mg

*Warning: May be habit forming

Acetaminophen, USP 300 mg

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

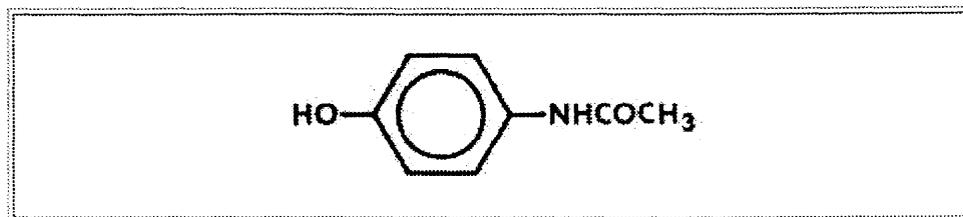
Butalbital (5-allyl-5-isobutylbarbituric acid), a slightly bitter, white, odorless, crystalline powder, is a short to intermediate-acting barbiturate. It has the following structural formula:



$C_{11}H_{16}N_2O_3$

MW = 224.26

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



$C_8H_9NO_2$

MW = 151.16

CLINICAL PHARMACOLOGY

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

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

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 25 mg/Acetaminophen 300 mg 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 25 mg/Acetaminophen 300 mg 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 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: 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 and acetaminophen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. These products 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: 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 and acetaminophen, 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 children below the age of 12 have not been established.

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, and seizures. 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.

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.

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 overdose of butalbital and acetaminophen, toxicity may result from the barbiturate or acetaminophen.

Signs and Symptoms: Toxicity from barbiturate poisoning include drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock.

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 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.

Treatment: A single or multiple overdose with these combination products 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	(40 tablets)
Acetaminophen: toxic dose 10 g	(33 tablets)

DOSAGE AND ADMINISTRATION

Butalbital 25 mg/Acetaminophen 300mg tablets: One or two tablets every four hours. Total daily dosage should not exceed 12 tablets.

Extended and repeated use of these products is not recommended because of the potential for physical dependence.

HOW SUPPLIED

Butalbital 25 mg/Acetaminophen 300 mg Tablets are supplied in bottles of 100 tablets, NDC 59702-253-01, and in bottles of 500, NDC 59702-253-05. Each tablet contains butalbital, USP 25 mg (Warning: May be habit forming) and acetaminophen, USP 300 mg. Tablets are uncoated, white, capsule-shaped and are embossed with "___" and scored "___" on one side.

Storage: Protect from light and moisture. Store at controlled room temperature, 15°-30°C (59°-86°F).

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

Rx only

Manufactured For:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005

Manufactured By:
PharmaFab
Grand Prairie, TX 75050

PIN ISS 12/01

Made in USA

x — No Varnish

NDC 59702-253-03

**Butalbital
25 mg
Acetaminophen
300 mg**

**Butalbital Acetaminophen
Tablets**

Each tablet contains:
Butalbital* 25 mg
Acetaminophen 300 mg

**Rx Only
500 Tablets**



WARNING: May be habit forming

USUAL ADULT DOSAGE: One or two tablets every four hours. Not recommended for use in children under 12.

Manufactured for:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005

ATBEY

THIS IS A BULK PACKAGE.
NOT INTENDED FOR HOUSEHOLD USE. PROTECT FROM LIGHT.
WARNING: Keep this and all drugs out of the reach of children.
STORAGE: Store at controlled room temperature 59-86°F (15-30°C) (see USP).
PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Manufactured by: **PharmaFab**, Grand Prairie, TX 75050
ISS 12/01
PSI

x — No Varnish

NDC 59702-253-01

**Butalbital
25 mg
Acetaminophen
300 mg**

**Butalbital Acetaminophen
Tablets**

Each tablet contains:
Butalbital* 25 mg
Acetaminophen 300 mg

**Rx Only
100 Tablets**



WARNING: May be habit forming

USUAL ADULT DOSAGE: One or two tablets every four hours. Not recommended for use in children under 12.

Manufactured for:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005

ATBEY

THIS IS A BULK PACKAGE.
NOT INTENDED FOR HOUSEHOLD USE. PROTECT FROM LIGHT.
WARNING: Keep this and all drugs out of the reach of children.
STORAGE: Store at controlled room temperature 59-86°F (15-30°C) (see USP).
PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Manufactured by: **PharmaFab**, Grand Prairie, TX 75050
ISS 12/01
PSI

Butalbital 50 mg/Acetaminophen 600 mg

Rx Only

CIII

DESCRIPTION

Butalbital 50 mg/Acetaminophen 600 mg is supplied in tablet form for oral administration.

Each Butalbital 50 mg/Acetaminophen 600 mg Tablet contains:

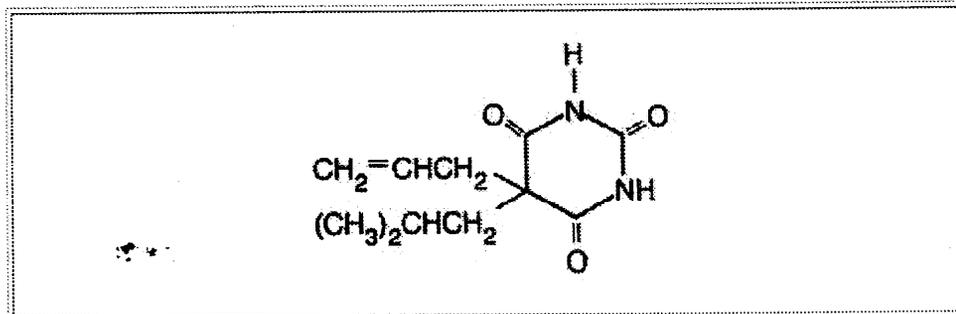
Butalbital*, USP50 mg

*Warning: May be habit forming

Acetaminophen, USP 600 mg

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

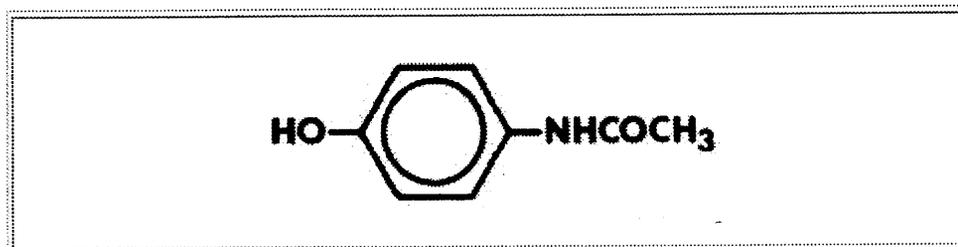
Butalbital (5-allyl-5-isobutylbarbituric acid), a slightly bitter, white, odorless, crystalline powder, is a short to intermediate-acting barbiturate. It has the following structural formula:



$\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_3$

MW = 224.26

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



$\text{C}_8\text{H}_9\text{NO}_2$

MW = 151.16

CLINICAL PHARMACOLOGY

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

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

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 50 mg/Acetaminophen 600 mg 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 50 mg/Acetaminophen 600 mg 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 50 mg/Acetaminophen 600 mg 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 and acetaminophen 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 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: 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 and acetaminophen, 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.

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, and seizures. 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.

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 a potential effect of the components of this product. Potential effects of high dosage are listed in the OVERDOSAGE section.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

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 and acetaminophen, toxicity may result from the barbiturate or the acetaminophen.

Signs and Symptoms: Toxicity from barbiturate poisoning include 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.

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	(16 tablets)

DOSAGE AND ADMINISTRATION

Butalbital 50 mg/Acetaminophen 600 mg: One tablet every four hours as needed. 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 50 mg/ Acetaminophen 600 mg Tablets are supplied in bottles of 100 tablets, NDC 59702-506-01, and in bottles of 500 tablets, NDC 59702-506-05. Each tablet contains butalbital, USP 50 mg (Warning: May be habit forming) and acetaminophen, USP 600 mg. Tablets are uncoated, white, capsule-shaped and are embossed with "___" and scored "___" on one side.

Storage: Protect from light and moisture. Store at controlled room temperature, 15° - 30°C (59° - 86°F).

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

Rx only

Manufactured For:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005

Manufactured By:
PharmaFab
Grand Prairie, TX 75050

PIN ISS 12/01

Made in USA

Manufactured for:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005



*** WARNING: May be habit forming**
USUAL ADULT DOSAGE: One tablet every four hours.
Not recommended for use in children under 12.

NDC 59702-508-05

Butalbital 50 mg Acetaminophen 600 mg

Butalbital Acetaminophen
Tablets

Each tablet contains:
Butalbital* 50 mg
Acetaminophen 600 mg

Rx Only
580 Tablets



THIS IS A BULK PACKAGE.
NOT INTENDED FOR HOUSEHOLD USE. PROTECT FROM LIGHT.
WARNING: Keep this and all drugs out of the reach of children.
STORAGE: Store at controlled room temperature 59-86°F (15-30°C) (see USP).
PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Manufactured by: **PharmaFab**, Grand Prairie, TX 75050
ISS 12/01
PSL

x — No Varnish

Manufactured for:
Atley Pharmaceuticals, Inc.
Ashland, VA 23005



*** WARNING: May be habit forming**
USUAL ADULT DOSAGE: One tablet every four hours.
Not recommended for use in children under 12.

NDC 59702-508-01

Butalbital 50 mg Acetaminophen 600 mg

Butalbital Acetaminophen
Tablets

Each tablet contains:
Butalbital* 50 mg
Acetaminophen 600 mg

Rx Only
100 Tablets



THIS IS A BULK PACKAGE.
NOT INTENDED FOR HOUSEHOLD USE. PROTECT FROM LIGHT.
WARNING: Keep this and all drugs out of the reach of children.
STORAGE: Store at controlled room temperature 59-86°F (15-30°C) (see USP).
PHARMACIST: Dispense in a tight, light-resistant container with a child-resistant closure.
Manufactured by: **PharmaFab**, Grand Prairie, TX 75050
ISS 12/01
PSL

x — No Varnish

ATT. 4

ATTACHMENT 4
REFERENCE LISTED DRUG LABELING

PHRENILIN®

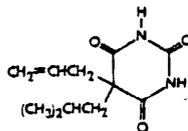
[fren'ī-lin]

(Butalbital® 50 mg and Acetaminophen 325 mg Tablet)
and**PHRENILIN® FORTE**(Butalbital® 50 mg and Acetaminophen 650 mg Capsule)
(WARNING—May be habit forming)**DESCRIPTION**

PHRENILIN®: Each PHRENILIN® tablet, for oral administration, contains Butalbital®, USP 50 mg (WARNING—May be habit forming), Acetaminophen, USP 325 mg. In addition each PHRENILIN® Tablet contains the following inactive ingredients: alginate acid, cornstarch, D&C Red No. 27—Aluminum Lake, FD&C Blue No. 1—Aluminum Lake, gelatin, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

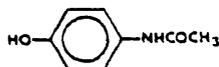
PHRENILIN® FORTE: Each PHRENILIN® FORTE capsule, for oral administration, contains Butalbital®, USP 50 mg (WARNING—May be habit forming), Acetaminophen, USP 650 mg.

In addition each PHRENILIN® FORTE capsule may also contain the following inactive ingredients: benzyl alcohol, butylparaben, D&C Red No. 28, D&C Red No. 33, edetate calcium disodium, FD&C Blue No. 1, FD&C Red No. 40, gelatin, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, sodium propionate and titanium dioxide. 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:

 $C_{11}H_{18}N_2O_3$

MW = 224.26

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

 $C_9H_9NO_2$

MW = 151.16

CLINICAL PHARMACOLOGY

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

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

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.

INDICATIONS AND USAGE

PHRENILIN® tablets & PHRENILIN® FORTE capsules 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: PHRENILIN® tablets & PHRENILIN® FORTE capsules (Butalbital 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, 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 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: 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 and acetaminophen can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. These products 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: 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 and acetaminophen, 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 children below the age of 12 have not been established.

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.

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.

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 and acetaminophen, toxicity may result from the barbiturate or acetaminophen.

Signs and Symptoms: Toxicity from barbiturate poisoning include 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 overdosage 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.

Treatment: A single or multiple overdose with these combination products 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 overdosage, 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):

PHRENILIN tablets (Butalbital 50 mg and Acetaminophen 325 mg tablets)

Butalbital: toxic dose 1 g (20 tablets)

Acetaminophen: toxic dose 10 g (30 tablets)

PHRENILIN FORTE capsules (Butalbital 50 mg and Acetaminophen 650 mg capsules)

Butalbital: toxic dose 1 g (20 capsules)

Acetaminophen: toxic dose 10 g (15 capsules)

DOSAGE AND ADMINISTRATION

PHRENILIN®: Oral: One or two tablets every four hours. Total daily dosage should not exceed 6 tablets.

PHRENILIN® FORTE: Oral: One capsule every four hours. Total daily dosage should not exceed 6 capsules.

Extended and repeated use of these products is not recommended because of the potential for physical dependence.

HOW SUPPLIED

PHRENILIN®: Pale violet scored tablets with the letter C on one side and 8650 on the other, in bottles of 100 (NDC 0086-0050-10). Each tablet contains butalbital, USP 50 mg (WARNING: May be habit forming) and acetaminophen, USP 325 mg.

PHRENILIN® FORTE: Amethyst, opaque capsules imprinted with the letter C and 8656, in bottles of 100 (NDC 0086-0056-10). Each capsule contains butalbital, USP 50 mg (WARNING: May be habit forming) and acetaminophen USP 650 mg.

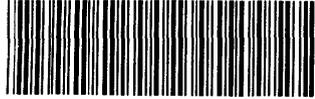
Store PHRENILIN® and PHRENILIN® FORTE (Butalbital and Acetaminophen) at controlled room temperature, 15°-30°C (59°-86°F). Dispense in a tight container as defined in the USP.

Caution: Federal Law Prohibits Dispensing Without Prescription

The most recent revision of this labeling is June 1993.
Manufactured for Carnrick Laboratories, Inc.

FROM: Paul Carr (972)355-9700
Shotwell & Carr, Inc.
3535 Firewheel Drive
Suite A
Flower Mound, TX 750282628

SHIPPER'S FEDEX ACCOUNT NUMBER



TO: Documents Management Branch (301)827-6869
Food and Drug Adm. (HFA-305)
12420 Parklawn Drive
Room 1-23

SHIP DATE: 30JAN02
MAN-WGT: 3 LBS

REF: #336
Rockville., MD 20857-



DELIVERY ADDRESS BARCODE (FEDEX-EDR)

CAD # 2526418

PRIORITY OVERNIGHT

THU
A2

PAK

TRK # 7902 9175 0685 FORM 0201

IAD

Deliver By:
31JAN02

20857-MD-US
DROP OFF

NZ GAIA

