BUPAP®
(Butalbital and Acetaminophen) TABLETS
50 mg/300 mg

Hepatotoxicity
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product.

DESCRIPTION
Each BUPAP Tablet for oral administration, contains Butalbital, USP 50 mg and Acetaminophen, USP 300 mg. In addition each BUPAP Tablet contains the following inactive ingredients: Pregelatinized Starch, Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate, D&C Yellow #10 Lake, and FD&C Red #40 Lake.

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:

\[
\text{C}_8\text{H}_9\text{NO}_2 \quad \text{M.W.}=151.16
\]

Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to the brain and other tissues in proportion to their fat content. The drug is excreted unchanged in the urine and in small amounts in the bile, and it is not removed by hemodialysis. The plasma half-life is approximately 2.5 hours. Elimination of butalbital is primarily via the kidney (95% to 98% of the dose), as unchanged drug or metabolites. The plasma half-life is about 3 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-allyl-5-(2,3-dihydroxy-propyl) barbituric acid (about 24% of the dose), and 5-allyl-5-hydroxy-2-methyl-1-propylbarbituric acid (about 4% of the dose).

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 disease and liver damage. Acetaminophen is metabolized in the liver via conjugation with sulfuric acid or glucuronic acid. Acetaminophen is excreted in the urine within 24 hours of administration, the majority as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

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. Pharmaco kinetics: The behavior of the individual components is described below.

Butalbital: Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to the brain and other tissues in proportion to their fat content. The drug is excreted unchanged in the urine and in small amounts in the bile, and it is not removed by hemodialysis. The plasma half-life is approximately 2.5 hours. Elimination of butalbital is primarily via the kidney (95% to 98% of the dose), as unchanged drug or metabolites. The plasma half-life is about 3 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-allyl-5-(2,3-dihydroxy-propyl) barbituric acid (about 24% of the dose), and 5-allyl-5-hydroxy-2-methyl-1-propylbarbituric acid (about 4% of the dose), products with the barbituric acid ring hydroxylized with hydroxylation of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% is conjugated.

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 disease and liver damage. Acetaminophen is metabolized in the liver via conjugation with sulfuric acid or glucuronic acid. Acetaminophen is excreted in the urine within 24 hours of administration, the majority as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

INDICATIONS AND USAGE
BUPAP Tablets are indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

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, tranquillizers such as chloral hydrate, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/labour 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 intoxicating feeling.

Infrequently Observed: Adverse events tabulated below are classified as infrequent.

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure</td>
<td>Infrequent</td>
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<tr>
<td>Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.</td>
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</tbody>
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REFERENCES
Acetaminophen: 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. However, it 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 the acetaminophen.

DOSAGE AND ADMINISTRATION
BUPAP Tablets: One or two tablets every four hours. Total daily dosage shall not exceed 6 tablets. Extended and repeated use of these products is not recommended because of the potential for physical dependence.

HOW SUPPLIED
Yellowish round, unscored tablets with BA 300 on one side and plain on the other. In bottles of 100 (NDC 0095-3000-01). Each tablet contains butalbital, USP 50 mg and acetaminophen, USP 300 mg. Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

For Medical Information or to report Adverse events
Phone 1-800-321-4576.

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