CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40267

APPROVAL LETTER

ANDA 40-267

JUL 30 1998

Watson Laboratories, Inc.
Attention: Ron Lapre
311 Bonnie Circle
Corona, CA 91720

Dear Sir:

This is in reference to your abbreviated new drug application dated August 4, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Butalbital, Acetaminophen and Caffeine Tablets USP, 50 mg/500 mg/40 mg.

Reference is also made to your amendment dated December 9, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Butalbital, Acetaminophen and Caffeine Tablets USP, 50 mg/500 mg/40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Esgic Plus™ Tablets, 500 mg/50 mg/40 mg, of Mikart, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7-30-98

cc: ANDA 40-267
Division File
FIELD COPY
HFD-600/Reading File
HFD-610/JPhillips
HFD-92
HFD-210/B.Poole
HFD-330/
HFD-205/F.O.I.

Endorsements:
HFD-645/R.Rajagopalan/1/23/98
HFD-645/B.Arnwine/3/2/98
HFD-617/K.Sherrod/2/19/98
HFD-613/J.Johnson/3/4/98
HFD-613/C.Hoppes/3/4/98

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F/T by pah/3/3/98 Revised:RLWest:7/29/98

APPROVAL LETTER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40267

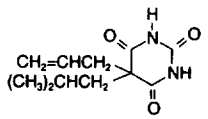
DRAFT FINAL PRINTED LABELING

BUTALBITAL, ACETAMINOPHEN AND CAFFEINE TABLETS, USP
50 mg/500 mg/40 mg

DESCRIPTION

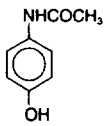
Butalbital, acetaminophen and caffeine is supplied in tablet form for oral administration.

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:



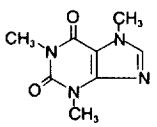
$C_{11}H_{16}N_2O_3$ MW=224.26

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=151.17

Caffeine (1,3,7-trimethylxanthine), a bitter, white crystalline 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 Butalbital, Acetaminophen and Caffeine Tablet contains:

Butalbital, USP ..... 50 mg

WARNING: May be habit forming

Acetaminophen, USP ..... 500 mg

Caffeine, USP ..... 40 mg

In addition each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, FD&C Blue #2 Aluminum Lake, microcrystalline cellulose, povidone, pregelatinized starch, sodium lauryl sulfate, 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% to 45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasm-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 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).

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-methyl-xanthine 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 tablets 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 tablets 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.

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.

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 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 42 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. 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 (20 tablets)

Caffeine:

toxic dose 1 g (25 tablets)

DOSAGE AND ADMINISTRATION

One tablet 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 are available as capsule shaped, light blue tablets debossed with WATSON 613 on one side and scored on the other side. Each tablet contains 50 mg butalbital (**Warning**: May be habit forming), 500 mg acetaminophen and 40 mg caffeine. They are supplied as follows:

Bottles of 100 tablets,	NDC#52544-613-01
Bottles of 500 tablets,	NDC# 52544-613-05

Store at controlled room temperature 15° to 30°C (59° to 86°F).

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

CAUTION: Federal law prohibits dispensing without prescription.

Watson Laboratories, Inc.
Corona, CA 91720

Revised: November 1997

NDC 52544-613-05

BUTALBITAL*, ACETAMINOPHEN and CAFFEINE TABLETS, USP

50 mg/500 mg/40 mg

***WARNING:** May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

WATSON LABORATORIES, INC.

Each Tablet Contains:
Butalbital, USP* ..... 50 mg
*Warning: May be habit forming.
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg
Dispense in a tight, light-resistant container with a child-resistant closure.

Usual Dose:
One tablet every four hours as needed. Do not exceed six tablets per day. See package insert for full information.

Warning: Keep this and all medications out of the reach of children.

Store at controlled room temperature
15° to 30°C (59° to 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

JUL 30 1996

N 3 52544-493-05 4

Lot No.:

Exp.:

NDC 52544-613-05

BUTALBITAL*, ACETAMINOPHEN and CAFFEINE TABLETS, USP

50 mg/500 mg/40 mg

*WARNING: May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

WATSON LABORATORIES, INC.

Each Tablet Contains:
Butalbital, USP* ..... 50 mg
*Warning: May be habit forming.
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg
Dispense in a tight, light-resistant container with a child-resistant closure.

Usual Dose:
One tablet every four hours as needed. Do not exceed six tablets per day. See package insert for full information.

Warning: Keep this and all medications out of the reach of children.

Store at controlled room temperature
15° to 30°C (59° to 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

30

N 3 52544-493-05 4

Lot No.:

Exp.:

NDC 52544-613-05

BUTALBITAL*, ACETAMINOPHEN and CAFFEINE TABLETS, USP

50 mg/500 mg/40 mg

*WARNING: May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

WATSON LABORATORIES, INC.

Each Tablet Contains:
Butalbital, USP* ..... 50 mg
*Warning: May be habit forming.
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg
Dispense in a tight, light-resistant container with a child-resistant closure.

Usual Dose:
One tablet every four hours as needed. Do not exceed six tablets per day. See package insert for full information.

Warning: Keep this and all medications out of the reach of children.

Store at controlled room temperature
15° to 30°C (59° to 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

30

N 3 52544-493-05 4

Lot No.:

Exp.:

NDC 52544-613-01

BUTALBITAL*, ACETAMINOPHEN and CAFFEINE TABLETS, USP

50 mg/500 mg/40 mg

***WARNING:** May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Butalbital, USP* ..... 50 mg
*Warning: May be habit forming.
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

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

Usual Dose:
One tablet every four hours as needed. Do not exceed six tablets per day. See package insert for full information.

Warning: Keep this and all medications out of the reach of children.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

JUL 30 1998

Lot No.:

Exp.:

NDC 52544-613-01

BUTALBITAL*, ACETAMINOPHEN and CAFFEINE TABLETS, USP

50 mg/500 mg/40 mg

***WARNING:** May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Butalbital, USP* ..... 50 mg
*Warning: May be habit forming.
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

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

Usual Dose:
One tablet every four hours as needed. Do not exceed six tablets per day. See package insert for full information.

Warning: Keep this and all medications out of the reach of children.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

JUL 30 1998

Lot No.:

Exp.:

NDC 52544-613-01

BUTALBITAL*, ACETAMINOPHEN and CAFFEINE TABLETS, USP

50 mg/500 mg/40 mg

***WARNING:** May be habit forming

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Butalbital, USP* ..... 50 mg
*Warning: May be habit forming.
Acetaminophen, USP ..... 500 mg
Caffeine, USP ..... 40 mg

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

Usual Dose:
One tablet every four hours as needed. Do not exceed six tablets per day. See package insert for full information.

Warning: Keep this and all medications out of the reach of children.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

Watson Laboratories, Inc.
Corona, CA 91720

JUL 30 1998

Lot No.:

Exp.:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40267

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA #: 40-267 **DRUG PRODUCT: Butalbital, Acetaminophen and Caffeine Tablets, USP** (50 mg/500 mg/40 mg)

FIRM: Watson Laboratories, Inc.

DOSAGE: Tablets

STRENGTH: 50 mg/500 mg/40 mg

cGMP STATEMENT/EIR UPDATE STATUS:
cGMP: GMP Certification (page # 188) is Adequate
EER: Pending.

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:
On 12/29/97 the Division of Bioequivalence issued a no comments letter to the firm.

METHODS VALIDATION(Including dosage form description):
Not required because it is a USP drug

STABILITY(Conditions, Containers, methods):
Bio batch

Specifications

TEST	SPECIFICATION
Appearance	Capsule shaped, light blue, compressed tablets debossed 'WATSON 613' on one side and scored on the other
Assay: (Butalbital) (Acetaminophen) (Caffeine)	% for each active
Dissolution: (Butalbital) (Acetaminophen) (Caffeine)	Q= % in 30 min for each active
Hardness	
Impurities Free (p-aminophenol) Single impurity (caffeine/ acetaminophen and butalbital) Total Impurities	 NMT % NMT % NMT %

Stability studies were done on the bio batch. Containers are the same as those listed in the container section (packaged in 500 count and 100 count). Stability studies are in conformance with the FDA Guidelines.

LABELING REVIEW STATUS: Satisfactory. See review dated 2/9/98.

STERILIZATION VALIDATION (If Applicable): N/A

BATCH SIZES:

BIO BATCH (identity #, DS source)

Batch #: R74796
Batch size: Tablets
NDS source:
Butalbital:
Acetaminophen:
Caffeine:

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)
Stability batch is the same as the bio batch

PROPOSED PRODUCTION BATCH
Tablets

Process is the same as the demonstration batch. Scale-up equipment is identified on page 207 of the ANDA. Reprocessing statement is also provided on page 208.

COMMENTS: Approvable

CHEMISTRY REVIEWER: **DATE:**

Radhika Rajagopalan January 23, 1998

/S/ 3/3/98

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-267

3. NAME AND ADDRESS OF APPLICANT
Watson Laboratories, Inc.
Attention: Ron Lapre
311 Bonnie Circle
Corona, CA 91720

4. BASIS OF SUBMISSION
The reference listed drug is Butalbital, Acetaminophen and Caffeine Tablets USP, 50 mg/500 mg/40 mg manufactured by Mikart, known as Esgic-Plus™.

Patent and exclusivity certification are provided (pages 15 and 17). In addition, firm states that the active ingredient, dosage form, strength, route of administration and conditions of use are the same as the listed drug.

6. PROPRIETARY NAME
Esgic-Plus™ Tablets

7. NONPROPRIETARY NAME
Butalbital, Acetaminophen and Caffeine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
08/04/97 - Original application
12/09/97 - ANDA Major amendment

FDA:
08/29/97 - ANDA Acknowledgment letter
12/6/96 - Correspondence by the Division of Bioequivalence
10/30/97- Chemistry and Labeling major deficiency letter
12/29/97- Biowaiver granted and communication from the Division of Bioequivalence

10. PHARMACOLOGICAL CATEGORY
Analgesic/Sedative

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF's:

13. DOSAGE FORM
Tablets

14. POTENCY
Butalbital/Acetaminophen/Caffeine
(50 mg/500 mg/40 mg)

15. CHEMICAL NAME AND STRUCTURE
Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)

Acetaminophen: N-(4-hydroxyphenyl)-acetamide ($C_3H_9NO_2$)

Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione ($C_3H_{10}N_4O_2$).

17. COMMENTS
All identified deficiencies are adequately addressed by the firm.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval of ANDA.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

DATE COMPLETED:
1/23/98

/S/ 3/3/98

/S/ 3/4/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40267

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-267 APPLICANT: Watson Laboratories, Inc.

DRUG PRODUCT: Acetaminophen/Butalbital/Caffeine 500 mg/ 50 mg/ 40 mg Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Acetaminophen/Butalbital/Caffeine	Watson Laboratories, Inc.
500 mg / 50 mg /40 mg Tablets	Corona, CA
ANDA # 40-267	Submission Date:
Reviewer: Moheb H. Makary	August 4, 1997
WP 40267D.897	

Review of Dissolution Data and Waiver Request

I. Objective:

The firm has requested a waiver of bioequivalence study requirements for its product Acetaminophen/Butalbital/Caffeine (500 mg / 50 mg /40 mg) Tablets. The firm has submitted dissolution test results in support of its request.

II. Formulation:

Watson's Acetaminophen/Butalbital/Caffeine 500 mg/50 mg/40 mg Tablets are shown in Table I.

III. Dissolution Data: (FDA Method)

The firm has submitted comparative dissolution data on its product Acetaminophen/Butalbital/Caffeine, 500 mg/50 mg/40 mg Tablets, and the listed reference drug product Esgic Plus™ Acetaminophen/ Butalbital/Caffeine, (500 mg/50 mg/40 mg) Tablets, manufactured by Mikart, Inc., using the following dissolution conditions:

Test product:	Watson's test product, lot #R74796
Method:	USP 23, apparatus II (paddle) at 50 rpm.
Medium:	900 mL of water
Number of Tablets:	12
Reference product:	Mikart's lot #950635E
Specifications:	NLT % in 30 minutes (all components).

Dissolution testing results are shown in Table II.

IV. Comments:

1. Dissolution results for Watson test product Acetaminophen/Butalbital/Caffeine, 500 mg/50 mg/40 mg Tablets is

Butalbital						
Sampling Times (Minutes)	Test Product Lot #R74796 Strength(mg) 50			Reference Product Lot #950635E Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
5	82.2		8.8	77.4		11.2
10	95.3		2.7	87.9		5.8
20	97.9		3.3	93.0		4.4
30	98.1		3.1	94.5		4.4

Caffeine						
Sampling Times (Minutes)	Test Product Lot #R74796 Strength(mg) 40			Reference Product Lot #950635E Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
5	79.6		8.5	78.7		13.2
10	94.9		1.9	89.6		6.7
20	97.7		2.1	94.4		3.9
30	98.4		1.9	96.1		3.0

acceptable as summarized in Table II.

2. Waiver of bioequivalence study requirements for the test product may be granted based on CFR 320.22 (c).

V. Recommendations:

1. The dissolution testing conducted by Watson, Laboratories, Inc., on its Acetaminophen/Butalbital/Caffeine, 500 mg/50 mg/40 mg Tablets, lot #R74796, is acceptable. Waiver of in vivo bioequivalence study requirements for the test product is granted based on CFR 320.22 (c). From the bioequivalence point of view, the Division of Bioequivalence deems Watson's Acetaminophen/Butalbital/Caffeine, 500 mg/50 mg/40 mg Tablets to be bioequivalent to Esgic Plus™ (Acetaminophen/Butalbital/Caffeine, 500 mg/50 mg/40 mg) Tablets manufactured by Mikart.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than % of all three components of the labeled amount of drug in the dosage form are dissolved in 30 minutes

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ -Date: 12/8/97

Concur: /S/ Date: 12/29/97

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

MM/10-24-97, 12-8-97, 40267D.897
cc: ANDA# 40-267 (original, duplicate) HFD-658 (Makary), Drug File, Division File.

Table II. In Vitro Dissolution Testing

Drug (Generic Name):Acetaminophen/Butalbital/Caffeine Tablets
Dose Strength:500 mg/50 mg/40 mg
ANDA No.:40-267
Firm: Watson
Submission Date: August 4, 1997

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of water
Specifications:NLT % in 30 minutes for all products
Reference Drug: Asgic Plus (Mikart) 500 mg/50 mg/40 mg Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing: Acetaminophen

Sampling Times (Minutes)	Test Product Lot #R74796 Strength(mg) 500			Reference Product Lot #950635E Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
5	84.1		8.4	71.9		5.9
10	95.6		1.7	83.8		4.1
20	97.5		1.6	88.4		3.2
30	98.0		1.5	89.9		2.9

Table I

Butalbital, Acetaminophen and Caffeine Tablets, USP
50 mg/ 500 mg/ 40 mg
ANDA

VII. 1. COMPONENTS AND COMPOSITION STATEMENT

INGREDIENT	STD	AMOUNT PER ANDA BATCH Lot R74796	AMOUNT PER TABLET (%)	AMOUNT PER TABLET (mg)	AMOUNT PER POST-APPROVAL BATCH (kg)
90% Acetaminophen, Anhydrous ** Compap®L	USP	kg			
Butalbital	USP	kg			
Caffeine, Anhydrous	USP	kg			
Crospovidone	NF	kg			
Colloidal Silicon Dioxide	NF	gm			
Sodium Lauryl Sulfate	NF	gm			
Anhydrous Lactose	NF	kg			
FD & C Blue # 2 Aluminum Lake 12%	House	gm			gm
Microcrystalline Cellulose	NF	kg			
Stearic Acid	NF	kg			
TOTAL		kg (tablets)	%	mg	kg (tablets)

* Equivalent to 500.0 mg of Acetaminophen.

** Compap®L contains the following inactive ingredients:

- Crospovidone, NF
- Povidone, NF
- Pregelatinized Starch, NF
- Stearic Acid, NF

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40267

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-267

Date of Submission: August 4, 1997

Applicant's Name: Watson Laboratories, Inc.

Established Name: Butalbital, Acetaminophen and Caffeine Tablets USP, 50 mg/500 mg/40 mg

Labeling Deficiencies:

1. CONTAINER: 100s and 500s

   a. Front Panel

      i. Add the statement "WARNING: May be habit forming" immediately beneath the established name. We refer you to 21 CFR 329.10(c) for further guidance.

      ii. ... dispensing without prescription.

   b. Side Panel

      i. We note your "Each tablet contains: ..." statement is not consistent with your DESCRIPTION section. Please revise and/or comment.

      ii. Delete and (500s size) from the side panel.

      iii. USUAL DOSAGE: ... every four hours ...

2. INSERT

   a. GENERAL COMMENT

      Please refer to the enclosed mocked-up pages of your draft insert labeling for further revisions.

   b. DESCRIPTION

      We note "FD&C Blue #2" is listed as an inactive ingredient in this DESCRIPTION section. However, your components and composition statement lists

"FD&C Blue# 2 Aluminum Lake". Please revise and/or comment.

c. CLINICAL PHARMACOLOGY (Pharmacokinetics)

Butabital

Revise the last paragraph to read as follows:

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.)

Please revise your labels and labeling, as instructed above, and submit final printed container labels, and final printed, (or draft if you prefer) insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Firm's mocked-up insert labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40267

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 9 1996

BY: REGULATORY AFFAIRS

DEC 5 1996

Watson Laboratories, Inc.
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona, California 91720

Reference number: Bio 96-235

Dear Dr. Hsia:

This letter is in response to your correspondence dated September 30, 1996, with inquiry for waiver of *in vivo* bioeqivalence study for Acetaminophen, Butalbital and Caffeine Tablets, 500 mg/50 mg/40 mg. The Office of Generic Drugs (OGD) has reviewed your request and the following comments are provided for your consideration:

1. The Information which you have supplied is correct. However, in addition to the Acetaminophen 325 mg and 650 mg with Butalbital and Caffeine tablets, the January - August, 1996 supplement to the "Orange book 16th Edition" indicates availability of Acetaminophen (500 mg), Butalbital (50 mg) and Caffeine (40 mg) tablet, manufactured by Mikart. Mikart's Acetaminophen (500 mg), Butalbital (50 mg) and Caffeine (40 mg) is the reference listed drug.

2. If your Acetaminophen (500 mg), Butalbital (50 mg) and Caffeine (40 mg) tablets demonstrate acceptable dissolution of each active component relative to the reference listed drug, manufactured by Mikart, a waiver of *in vivo* bioequivalence study can be granted.

The comments provided in this correspondence are based on the submitted scientific information and the proposed issue(s) at hand. The Office may modify the bioequivalence testing requirements if needed.

If you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-267

Watson Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona, CA 91720

AUG 29 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Butalbital, Acetaminophen and Caffein Tablets USP, 50 mg/500 mg/40 mg

DATE OF APPLICATION: 4 August 1997

DATE OF RECEIPT: 6 August 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips 8/28/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

August 4, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: **Abbreviated New Drug Application**
BUTALBITAL, ACETAMINOPHEN AND CAFFEINE TABLETS, USP
50 mg/500 mg/40 mg

Dear Mr. Sporn:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.92, Watson Laboratories Inc. submits herein an original Abbreviated New Drug Application for Butalbital, Acetaminophen and Caffeine Tablets, USP 50 mg/500 mg/ 40 mg.

The drug product described above is the same as Esgic-Plus ™ (Butalbital, Acetaminophen and Caffeine Tablets in the "Orange book 17th Edition") from Mikart, Inc. Comparative information is being provided to show that our product is the same as the reference listed drug product. This information is presented in tabular form comparing active ingredient, conditions of use, route of administration, dosage form, strength, and labeling for the products as supplied by Watson Laboratories, Inc. and Mikart, Inc.

Based on the attached FDA correspondence dated December 5, 1996, a request for waiver of *in vivo* bioequivalence study is included in Section VI as acceptable dissolution of each active component relative to the listed drug has been demonstrated (see Section VI).

We have enclosed one (1) archival, one (1) review, and in accordance with 21 CFR §314.94(5), one (1) field copy of the application will be forwarded to the LA District Office.

Watson Laboratories Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application.

As required, three (3) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA.

The number of volume in the archival, review, and field copies of the ANDA are as follows:

Blue Archival Copy	- 1 volume
Orange Review Copy	- 1 volume
Red Review Copy	- 1 volume
Burgundy Field Copy	- 1 volume

We trust that the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. Please contact me by phone at (909) 270-1400 or by fax at (909) 270-1428 if you have any questions or if I can assist you with the review of this application.

Sincerely,

David C. Hsia

David C. Hsia, Ph.D.
Executive V. P., Research and Development
WATSON LABORATORIES, INC.

ARCHIVAL COPY

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

December 9, 1997

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place Room 150
Rockville, MD 20855-2773

Major Amendment

Re: ANDA 40-267
BUTALBITAL, ACETAMINOPHEN AND CAFFEINE TABLETS, USP
50 mg/500 mg/40 mg

INCLUDE FINAL PRINTED LABELING

Dear Mr. Sporn:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.96, Watson Laboratories is submitting this major amendment to provide a complete response to the comments included in the FDA letter dated October 30, 1997 (copy attached) pertaining to the referenced ANDA. Our responses are given in the order in which the comments appear in the letter. This amendment also includes final printed labeling.

We have enclosed one (1) archival, one (1) review copy, and in accordance with 21 CFR §314.96(b), one (1) field copy of the application will be forwarded to the FDA Los Angeles District Office.

Watson Laboratories, Inc. certifies that the Field copy is a true copy of the technical section contained in this amendment.

We trust this information is sufficient for this amendment to be evaluated. If I can assist with the review of this application, please contact me by phone at (909) 270-1400 or by fax at (909) 270-1428.

Sincerely,

Ron Lapré
Senior Director
Regulatory Affairs

RECEIVED
DEC 10 1997
GENERIC DRUGS

311 Bonnie Circle, Corona, California 91720 • Tel: 909/270-1400 • Fax: 909/270-1096

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

December 9, 1997

Ms. Elaine C. Messa
District Director
Food & Drug Administration
19900 MacArthur Blvd., Suite 300
Irvine, CA 92715

Major Amendment

RE: **Field Copy**
ANDA 40-267
BUTALBITAL, ACETAMINOPHEN AND CAFFEINE TABLETS, USP
50 mg/500 mg/40 mg

Dear Ms. Messa:

Pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.96, Watson Laboratories has submitted an amendment to the referenced ANDA to the Office of Generic Drugs. In accordance with 21 CFR §314.96(b), Watson is providing the enclosed Field Copy (1 volume) of the amendment to the LA District Office.

Watson Laboratories certifies that this Field copy is a true copy of the technical section of the Butalbital, Acetaminophen and Caffeine Tablets, USP 50 mg/500 mg/40 mg Major Amendment submitted to the Office of Generic Drugs on December 9, 1997.

Please call me at (909) 270-1400 if you have any questions regarding this submission.

Sincerely,

Ron Lapré
Senior Director
Regulatory Affairs

311 Bonnie Circle, Corona, California 91720 • Tel: 909/270-1400 • Fax: 909/270-1096