CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 040885

Name: Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/300 mg/40 mg

Sponsor: Nexgen Pharma, Inc

Approval Date: November 16, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA040885Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Pharm/Tox Review	
Bioequivalence Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	**X**
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040885

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 040885

Nexgen Pharma, Inc.
Attention: Robert van Osdel
Vice President, Scientific Affairs
17802 Gillete Avenue
Irvine, CA 92614-6502

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 20, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/300 mg/40 mg.

Reference is made to your amendments dated December 4, 2007; February 20, June 3, 2008; and March 9, September 11, and September 17, 2009. Reference is also made to the ANDA Suitability Petition (2004P-0561/CP1) submitted under Section 505(j)(2)(c) of the Act and approved by this office on March 31, 2005. This petition permitted the agency to file this ANDA for a drug product that differs in strength from the reference listed drug product (RLD). Specifically, 300 mg of the acetaminophen component is present in your drug product vs. 325 mg in the Mikart's RLD as noted below.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined that your Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/300 mg/40 mg, can be expected to have the same therapeutic effect as that of the reference listed drug, (RLD), Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/325 mg/40 mg of Mikart, Inc., upon which the agency relied

as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in

content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as ***"Miscellaneous Correspondence – SPL for Approved ANDA 040885".***

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-40885	ORIG-1	ANABOLIC LABORATORIES INC	BUTALBITAL;ACETAMINOPHEN ;CAFFEINE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST
11/16/2009
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040885

LABELING

nexgen pharma™

NDC 0722-7029-01

Butalbital, Acetaminophen, and Caffeine Capsules, USP

Each Capsule Contains:

Butalbital USP	50 mg
WARNING: May be habit forming	
Acetaminophen USP	300 mg
Caffeine USP	40 mg

Rx only **100 Capsules**

DOSAGE AND ADMINISTRATION:

Usual Adult Dosage: 1 or 2 capsules every four hours. Total daily dose should not exceed 6 capsules. See package insert for additional prescribing information.

Store and Dispense: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature Dispense in a tight light resistant container

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Mfg by Nexgen Pharma nc rvine California 92614

Rev 04/07

Lot No Exp Date

3 07227 02901 3

nexgen pharma™

NDC 0722-7029-05

Butalbital, Acetaminophen, and Caffeine Capsules, USP

Each Capsule Contains:

Butalbital USP	50 mg

WARNING: May be habit forming

Acetaminophen USP	300 mg
Caffeine USP	40 mg

Rx only

500 Capsules

DOSAGE AND ADMINISTRATION:
Usual Adult Dosage: 1 or 2 capsules every four hours Total daily dose should not exceed 6 capsules See package insert for additional prescribing information

Store and Dispense: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature Dispense in a tight light resistant container

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Mfg by Nexgen Pharma nc rvine California 92614
Rev 04/07

Lot No Exp Date

3 07227 02905 1

Butalbital, Acetaminophen, and Caffeine Capsules USP

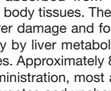
DESCRIPTION
Butalbital, Acetaminophen and Caffeine Capsules USP are supplied in hard-gelatin capsule form for oral administration.

Each capsule contains the following active ingredients:
Butalbital, USP..... 50 mg
Acetaminophen, USP..... 300 mg
Caffeine, USP..... 40 mg

Inactive Ingredients: sodium lauryl sulfate, talc, microcrystalline cellulose, and stearic acid.

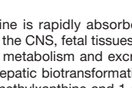
Butalbital (5-allyl-5-isobutylbarbituric acid), is a short to intermediate-acting barbiturate. It has the following structural formula:

$C_{11}H_{16}N_2O_3$
Mol. wt. 212.25



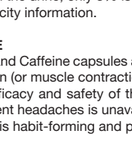
Acetaminophen (4´-hydroxyacetanilide), is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

$C_8H_9NO_2$
Mol. wt. 151.16



Caffeine (1,3,7-trimethylxanthine), is a central nervous system stimulant. It has the following structural formula:

$C_8H_{10}N_4O_2$
Mol. wt. 194.19



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 0.5-20 mcg/mL. This falls within the range of plasma protein binding (20%-45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity, indicating that there is no preferential distribution of butalbital into either plasma or blood cells.
See **OVERDOSAGE** for toxicity information.

Acetaminophen
Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following 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-methylxanthine and 1-methyluric acid. Of the 70% of the dose that is recovered in the urine, only 3% is unchanged drug.
See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE
Butalbital, Acetaminophen and Caffeine 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
Butalbital, acetaminophen, and caffeine capsules 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.
For information on use in geriatric patients, see PRECAUTIONS/Geriatric Use.

Laboratory Tests
In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions
The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.
Butalbital, acetaminophen, and caffeine may enhance the effects of: other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions
Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No adequate studies have been conducted in animals to determine whether acetaminophen or butalbital have a potential for carcinogenesis, mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects
Pregnancy Category C: Animal reproduction studies have not been conducted with this combination product. It is also not known whether butalbital, acetaminophen, and caffeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This product should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects
Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last two months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Nursing Mothers
Caffeine, barbiturates, and acetaminophen are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from butalbital, acetaminophen, and caffeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use
Clinical studies of butalbital, acetaminophen and caffeine capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Butalbital is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Frequently Observed
The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

Infrequently Observed
All adverse events tabulated below are classified as infrequent.
Central Nervous System: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure. Mental confusion, excitement, or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.
Autonomic Nervous System: dry mouth, hyperhidrosis.
Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.
Cardiovascular: tachycardia.
Musculoskeletal: leg pain, muscle fatigue.
Genitourinary: diuresis.
Miscellaneous: pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.
Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported.
The following adverse drug events may be borne in mind as potential effects of the components of this product. Potential effects of high dosage are listed in the OVERDOSAGE section.
Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.
Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

DRUG ABUSE AND DEPENDENCE

Abuse and Dependence

Butalbital
Barbiturates may be habit-forming: Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE
Following an acute overdosage of butalbital, acetaminophen, and caffeine, toxicity may result from the barbiturate or the acetaminophen. Toxicity due to caffeine is less likely, due to the relatively small amounts in this formulation.

Signs and Symptoms
Toxicity from ***barbiturate*** poisoning 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.
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 capsules)
Acetaminophen: Toxic dose 10 g (33 capsules)
Caffeine: Toxic dose 1 g (25 capsules)
In all cases of suspected overdosage, call your Regional Poison Control Center to obtain the most up-to-date information about the treatment of overdosage. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®*.

DOSAGE AND ADMINISTRATION
One or 2 capsules every 4 hours as needed. Total daily dosage should not exceed 6 capsules.
Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED
Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg
Containing 50 mg butalbital, 300 mg acetaminophen, and 40 mg caffeine. Available as hard gelatin capsules with a green cap, printed with NXG, and a yellow body, printed with 7029. The capsules are supplied in bottles of 100 capsules (NDC 00722-7029-01) and 500 capsules (NDC 00722-7029-05.
Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]; Dispense in a tight, light-resistant container.
*Trademark of Medical Economics Company, Inc.

Rx only

Nexgen Pharma Inc.
Irvine, CA 92614-6502 USA

Rev 01/07

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040885

LABELING REVIEWS

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-885 Date of Submission: June 3, 2008

Applicant's Name: Nexgen Pharma, Inc.

Established Name: Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

CONTAINER LABELS - 100s and 500s

Satisfactory in FPL as of the 6/3/08 submission

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of the 6/3/08 submission

Satisfactory in SPL as of the 6/3/08 submission

FOR THE RECORD:

1. MODEL LABELING - The review was done using the labeling submitted in the annual report of 2006 for ANDA 89-007 (Butalbital, APAP, and Caffeine Capsules USP, 50 mg/325 mg/40 mg). This is the new RLD as Esgic Capsules (ANDA 89-660) was discontinued. It was last approved on 10/15/1993 (ANDA 89-007/S-026). In addition, the Fioricet® Tablets (ANDA 88-616/S-041, approved 7/18/02), which has the same strength/combination as ANDA 89-007, was also used for review.

2. This application of new strength was accepted for filing through C.P. The acceptance date is March 31, 2005 (Docket 2004P-0561)

3. This drug product is the subject of a USP monograph.

4. The sponsor withdrew the proposal for the proprietary name, " (b) (4) in the submission of 6/3/08.

5. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 3.2.9.2.

6. PATENTS/EXCLUSIVITIES

   None exists.

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD - Store at controlled room temperature, 15oC to 30oC (50oF to 46oF) [see USP]

   ANDA: Store at 20 to 25^{o}C (68 to 77^{o}F) in tight, light-resistant container. [see USP Controlled Room Temperature]. See comment under container.

   USP - Preserve in tight containers

8. PACKAGING CONFIGURATIONS

RLD - 100s

ANDA - 100s and 500s

9. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See section 3.2.p.5.1

10. CONTAINER/CLOSURE (section 3.2.p.7)

Container - HDPE
Closure - Plastic White Polypropylene Cap with (b) (4) Seal

11. Manufacturer - Nexgen Pharma, Inc. (section 3.2.p.3.1)

12. The SPL submitted 4/20/07 failed validation. See comment 1(d) above.

13. I sent the following e-mail to PM regarding RLD.

From: Park, Chan H
Sent: Tuesday, July 31, 2007 3:28 PM
To: Longstaff, Laura
Cc: Shimer, Martin; Golson, Lillie D
Subject: 40-885 (Butalbital, APAP, and Caffeine Capsules, 50 mg/300mg/40 mg)

Hi Laura,

We note that this application for new strength (e.g. APAP 300 mg) is accepted for filing through CP and was based on the Esgic capsules (ANDA **89-660**, 50 mg/325 mg/40 mg)). However, Esgic® Capsules was discontinued and ANDA **89-007** is the same strength as Esgic® and became the new RLD for this combination. The sponsor put Esgic capsules (ANDA 89-007) on the 356h form*, i.e.* correct ANDA number but wrong name. The new ANDA-RLD 89-007 does not have a proprietary name. I will inform the sponsor of this. Since the discontinued Esgic and new ANDA-RLD 89-007 have the same strength, this mistake should not affect the review of this application. All they have to do is to take off the name "Esgic" from the application form, I guess. Thanks,

Chan

14. The sponsor corrected the errors in the DLDE as requested in the last deficiency letter.

15. The following e-mail is to/from DAARP:

From: Park, Chan H
Sent: Wednesday, April 09, 2008 10:35 AM
To: Clayton, Tanya
Cc: Golson, Lillie D
Subject: 20-232/s-021 (Fioricet with codeine)

Hi Tanya,

I note that this was approved 3/21/08 with revisions in many different sections. The RLD for Fioricet tablets is an ANDA (88-616) and the labeling was last approved in 2002. I wonder the updated Fioricet with Codeine labeling would affect the plain Fioricet labeling (apart from the new information regarding codeine). Please advise. Thanks, Chan

---

From: Clayton, Tanya
Sent: Wednesday, April 09, 2008 10:43 AM
To: Park, Chan H
Cc: Golson, Lillie D
Subject: RE: 20-232/s-021 (Fioricet with codeine)

Hi Chan,

I did numerous researches for this when I was working on the labeling and I was told there was no ANDA associated with this. All labeling for Codeine products have been updated. The additional changes made was to make changes that the previous sponsors failed to make. (b) (4)

(b) (4)

Hope this helps,

Tanya D.Clayton
Regulatory Health Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, & Rheumatology Products
(301) 796-0871 Phone
Tanya.Clayton@fda.hhs.gov

Date of Review: 10/9/08 **Date of Submission: 6/3/08**

Primary Reviewer: Chan Park **Date:**

Team Leader: Lillie Golson **Date:**

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chan Park
10/15/2008 07:53:50 AM
LABELING REVIEWER

Lillie Golson
10/16/2008 04:59:57 PM
LABELING REVIEWER

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

ANDA Number: 40-885 Date of Submission: February 20, 2008

Applicant's Name: Nexgen Pharma, Inc.

Established Name: Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg

Proposed Proprietary Name: (b) (4)

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We note that contrary to your statement, you still have the ANDA 89-660 as the RLD in your application. As addressed in the last deficiency letter, the "Esgic® Capsules (ANDA 89-660)" has been discontinued and the new RLD is the ANDA 89-007 (Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg). Please note that the new RLD does not have a proprietary name. Please revise your application form accordingly.

   b. Your proposed proprietary name, (b) (4) is still under review by the Office of Surveillance and Epidemiology. We will inform you of the comments when available.

2. CONTAINER - 100s and 500s

   a. See GENERAL COMMENT (a) above.

   b. Your proposed proprietary name appears much larger than the established name. Please note that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.

   c. Please ensure that all text appears sufficiently legible, particularly the "Usual Adult Dosage" section.

   d. Please note that for computer generated labeling to be acceptable as final print, it must be of actual size, color, and clarity. Please ensure that these criteria are met prior to submission of final print.

3. INSERT

   a. See GENERAL COMMENT (a) above.

   b. Please be advised that the requirements of 21 CFR 201.10(g) must be met. The established name must appear in certain sections in association with the proprietary name if the proprietary name is approved and used in the text.

We will not request the submission of the final printed labeling pending the review of your proposed proprietary name.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

FOR THE RECORD:

1. MODEL LABELING - The review was done using the labeling submitted in the annual report of 2006 for ANDA 89-007 (Butalbital, APAP, and Caffeine Capsules USP, 50 mg/325 mg/40 mg). This is the new RLD as Esgic Capsules (ANDA 89-660) was discontinued. It was last approved on 10/15/1993 (ANDA 89-007/S-026). In addition, the Fioricet® Tablets (ANDA 88-616/S-041, approved 7/18/02), which has the same strength/combination as ANDA 89-007, was also used for review.

2. This application of new strength was accepted for filing through C.P. The acceptance date is March 31, 2005 (Docket 2004P-0561)

3. This drug product is the subject of a USP monograph.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 3.2.9.2.

5. PATENTS/EXCLUSIVITIES

   None exists.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD - Store at controlled room temperature, 15oC to 30oC (50oF to 46oF) [see USP]

   ANDA: Store at 20 to 25^{o}C (68 to 77^{o}F) in tight, light-resistant container. [see USP Controlled Room Temperature]. See comment under container.

   USP - Preserve in tight containers

7. PACKAGING CONFIGURATIONS

   RLD - 100s

   ANDA - 100s and 500s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See section 3.2.p.5.1

9. CONTAINER/CLOSURE (section 3.2.p.7)

   Container - HDPE
   Closure - Plastic White Polypropylene Cap with (b) (4) Seal

10. Manufacturer - Nexgen Pharma, Inc. (section 3.2.p.3.1)

11. The SPL submitted 4/20/07 failed validation. See comment 1(d) above.

12. I sent the following e-mail to PM regarding RLD.

From: Park, Chan H
Sent: Tuesday, July 31, 2007 3:28 PM
To: Longstaff, Laura
Cc: Shimer, Martin; Golson, Lillie D
Subject: 40-885 (Butalbital, APAP, and Caffeine Capsules, 50 mg/300mg/40 mg)

Hi Laura,

We note that this application for new strength (e.g. APAP 300 mg) is accepted for filing through CP and was based on the Esgic capsules (ANDA **89-660**, 50 mg/325 mg/40 mg)). However, Esgic® Capsules was discontinued and ANDA **89-007** is the same strength as Esgic® and became the new RLD for this combination. The sponsor put Esgic capsules (ANDA 89-007) on the 356h form, *i.e.* correct ANDA number but wrong name. The new ANDA-RLD 89-007 does not have a proprietary name. I will inform the sponsor of this. Since the discontinued Esgic and new ANDA-RLD 89-007 have the same strength, this mistake should not affect the review of this application. All they have to do is to take off the name "Esgic" from the application form, I guess. Thanks,

Chan

13. The sponsor corrected the errors in the DLDE as requested in the last deficiency letter.

14. The following e-mail is to/from DAARP:

From: Park, Chan H
Sent: Wednesday, April 09, 2008 10:35 AM
To: Clayton, Tanya
Cc: Golson, Lillie D
Subject: 20-232/s-021 (Fioricet with codeine)

Hi Tanya,

I note that this was approved 3/21/08 with revisions in many different sections. The RLD for Fioricet tablets is an ANDA (88-616) and the labeling was last approved in 2002. I wonder the updated Fioricet with Codeine labeling would affect the plain Fioricet labeling (apart from the new information regarding codeine). Please advise. Thanks, Chan

---

From: Clayton, Tanya
Sent: Wednesday, April 09, 2008 10:43 AM
To: Park, Chan H
Cc: Golson, Lillie D
Subject: RE: 20-232/s-021 (Fioricet with codeine)

Hi Chan,

I did numerous researches for this when I was working on the labeling and I was told there was no ANDA associated with this. All labeling for Codeine products have been updated. The additional changes made was to make changes that the previous sponsors failed to make. (b) (4)

(b) (4)

Hope this helps,
Tanya D.Clayton
Regulatory Health Project Manager
Food and Drug Administration
Division of Anesthesia, Analgesia, & Rheumatology Products
(301) 796-0871 Phone
Tanya.Clayton@fda.hhs.gov

Date of Review: 4/9/08 **Date of Submission: 2/20/08**

Primary Reviewer: Chan Park **Date:**

Team Leader: Lillie Golson **Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chan Park
4/11/2008 09:46:35 AM
LABELING REVIEWER

Lillie Golson
4/11/2008 11:43:25 AM
LABELING REVIEWER

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

ANDA Number: 40-885 Date of Submission: April 20, 2007

Applicant's Name: Nexgen Pharma, Inc.

Established Name: Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg

Proposed Proprietary Name: (b) (4)

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. In your application form, you entered "Esgic® Capsules (89-007)" as the Reference Listed Drug for the basis for submission of this application. Please note that the ANDA for Esgic® capsules is 89-660, not 89-007. It appears that Esgic capsules (89-660) have been discontinued per the Electronic Orange Book. The ANDA 89-007 was assigned as a new RLD for Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/325 mg/40 mg. Please revise the application form accordingly.

   b. Your proposed proprietary name, (b) (4) was forwarded to the Office of Surveillance and Epidemiology for their review and comments. We will inform you of the comments when available.

   c. We note that you submitted your proposed insert labeling in SPL only. Please be advised that you still need to include the pdf. version in final printed format for approval. In addition, please include the MS Word version for ease of review.

   d. It appears that your SPL submitted failed validation. Please contact the SPL group at SPL@fda.hhs.gov for detail.

2. CONTAINER - 100s and 500s

   a. Revise to read as follows:

      Store and Dispense: Store at 20 to 25°C (68 to 77°C) [see USP Controlled Room Temperature] Dispense in a tight, light-resistant container.

   b. Please ensure that you complete the bar code prior to the submission of final printed labels.

3. INSERT

   a. DESCRIPTION

      i. Revise the molecular weight of butalbital to read "212.25 per the USP 30.

      ii. Revise the molecular weight of acetaminophen to read "151.16" per the USP 30.

   b. OVERDOSAGE - Toxic Doses (for adults), Acetaminophen:

      As your proposed formulation contains 300 mg of acetaminophen, not (b) (4), it should read "(33 capsules)" rather than (b) (4). Please revise and/or comment.

c. HOW SUPPLIED

i. First paragraph - Revise to read as follows:

Butalbital, Acetaminophen, and Caffeine Capsules USP,
50 mg/300 mg/40 mg

ii. Second paragraph - Revise to read:

Containing 50 mg butalbital, 300 mg acetaminophen, and 40 mg caffeine… [rather than (b) (4)

iii. We encourage the inclusion of NDC numbers.

d. DATA ELEMENT TABLE

i. Product name - Revise to read as follows, if your proposed name is found acceptable:

(b) (4)

ii. Ingredients

Delete the term (b) (4) associated with the ingredients.

iii. Appearance - Symbol:

We believe that your finished drug product does not contain the "symbol", but contains the imprint code only. Please revise to read (b) (4) rather than (b) (4)

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

FOR THE RECORD:

1. MODEL LABELING - Esgic® Capsules. However, see the GENERAL COMMENT 1(a) above. The review was done using the labeling submitted in the annual report of 2006 for ANDA 89-007 (Butalbital, APAP, and Caffeine Capsules USP, 50 mg/325 mg/40 mg). It was last approved on 10/15/1993 (ANDA 89-007/S-026). In addition, the Fioricet® Tablets (ANDA 88-616/S-041, approved 7/18/02), which has the same strength/combination as ANDA 89-007, was also used for review.

2. This application of new strength was accepted for filing through C.P. The acceptance date is March 31, 2005 (Docket 2004P-0561)

3. This drug product is the subject of a USP monograph.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and

composition appearing in section 3.2.9.2.

5. PATENTS/EXCLUSIVITIES

None exists.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store at controlled room temperature, 15oC to 30oC (50oF to 46oF) [see USP]

ANDA: Store at 20 to 25°C (68 to 77°F) in tight, light-resistant container. [see USP Controlled Room Temperature]. See comment under container.

USP - Preserve in tight containers

7. PACKAGING CONFIGURATIONS

RLD - 100s

ANDA - 100s and 500s

8. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See section 3.2.p.5.1

9. CONTAINER/CLOSURE (section 3.2.p.7)

Container - HDPE
Closure - Plastic White Polypropylene Cap with (b) (4) Seal

10. Manufacturer - Nexgen Pharma, Inc. (section 3.2.p.3.1)

11. The SPL submitted 4/20/07 failed validation. See comment 1(d) above.

12. I sent the following e-mail to PM regarding RLD.

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Sent: Tuesday, July 31, 2007 3:28 PM
To: Longstaff, Laura
Cc: Shimer, Martin; Golson, Lillie D
Subject: 40-885 (Butalbital, APAP, and Caffeine Capsules, 50 mg/300mg/40 mg)

Hi Laura,

We note that this application for new strength (e.g. APAP 300 mg) is accepted for filing through CP and was based on the Esgic capsules (ANDA **89-660**, 50 mg/325 mg/40 mg)). However, Esgic was discontinued and ANDA **89-007** is the same strength as Esgic and became the new RLD for this combination. The sponsor put Esgic capsules (ANDA 89-007) on the 356h form*, i.e.* correct ANDA number but wrong name. The new ANDA-RLD 89-007 does not have a proprietary name. I will inform the sponsor of this. Since the discontinued Esgic and new ANDA-RLD 89-007 have the same strength, this mistake should not affect the review of this application. All they have to do is to take off the name "Esgic" from the application form, I guess. Thanks,

Chan

Date of Review: 8/1/07 **Date of Submission: 4/20/07**

Primary Reviewer: Chan Park **Date:**

Team Leader: Lillie Golson **Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chan Park
8/6/2007 10:56:24 AM
LABELING REVIEWER

Jacqueline Council
8/6/2007 02:57:19 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040885

CHEMISTRY REVIEWS

ANDA 40-885

Butalbital, Acetaminophen, and Caffeine Capsules USP,
50 mg/300 mg/40 mg

Nexgen Pharma, Inc.

Lucia C. Tang
OGD, DC II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 40-885

2. REVIEW # 3

3. REVIEW DATE: 9-7-09 , revised 9-18-09

4. REVIEWER: Lucia C. Tang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm:	
Original Submission	4-20-07
Communication and Correspondence	7-10-07
Acceptable for filing	4-23-07
Amendment	5-23-08
Amendment	3-9-09
Amendment (WD XOVA testing site)	9-11-09
Amendment	9-17-09
FDA	
Acknowledgment	7-13-07
1st NA letter	3-6-08
2nd NA letter	12-23-08
Tel-con regarding USP <467>	9-10-09

6. SUBMISSION(S) BEING REVIEWED:

Source	Submission(s) Reviewed	Document Date
Firm:	Amendment Amendment	March 9, 2009 September 17, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Nexgen Pharma, Inc.

Address: 17802 Gillette Avenue
Irvine, CA 92614-6502
Attention: Robert van Osdel

Representative: Robert van Osdel

Chemistry Review Data Sheet

Telephone: 949 260-3704
Facsimile: 949 261-2787

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Butalbital, Acetaminophen, and Caffeine Capsules

9. LEGAL BASIS FOR SUBMISSION:

The reference listed Acetaminophen, Butalbital, and Caffeine Capsules USP, 325 mg/50 mg/ 40 mg was approved for Mikart, Inc. on March 17, 1986 (ANDA # 89007).

10. PHARMACOL. CATEGORY : Analgesic/Sedative
Relief of the symptom complex of tension headache

11. DOSAGE FORM: Hard Gel Capsules

12. STRENGTH/POTENCY: 50 mg/300 mg/40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen: N-(4-hydroxyphenyl)-Acetamide (b) (4)

Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione
(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	***Adequate***	***7-28-09***	***L. Tang***
	II			3	***Adequate***	***7-7-09***	***S. Bain***
	II			3	***Adequate***	***7-22-09***	***R. Power***
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION N`UMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	4-2-08	OC
Methods Validation	N/A per OGD policy		
Labeling	Satisfactory	10-16-08	C. Park
Bioequivalence	Satisfactory	2-28-08	P. Nwakama
EA	Exclusion under 21 CFR 25.31(a)		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ___ No If no, explain reason(s) below:

Executive Summary Section

The Chemistry Review for ANDA 40-885

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Application is approvable for the following reasons:

Chemistry: Satisfactory per L. Tang on 9-17-09
Labeling: Satisfactory per C. Park reviewed on 10-9-08
Bioequivalence: Satisfactory per P. Nwakama reviewed on 2-28-2008.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Chemical names:
Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen: N-(4-hydroxyphenyl)-Acetamide (b) (4)
Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione (b) (4)

Drug substance Butalbital USP is a White, odorless, crystalline powder . The melting point is (b) (4)

Acetaminophen USP is a White, odorless, free-flowing granular powder, having a slightly bitter taste. (b) (4)

Caffeine USP is a White powder or white glistening needles, (b) (4), is odorless and has a bitter taste. (b) (4)

Drug Product: Butalbital, Acetaminophen, and Caffeine Capsules, USP, 50 mg/300 mg/40 mg
Description: #0 gelatin capsule, green cap, yellow body, filled with white powder

The manufacture of Butalbital, Acetaminophen, and Caffeine Capsules, USP

(b) (4)

Packaging: Butalbital, Acetaminophen, and Caffeine Capsules, USP, 50mg/300mg/40mg is packaged in 100's and 500's packaged sizes

Store at 20 to 25ºC (68 to 77ºC) [see USP Controlled Room Temperature] Dispense in a tight, light-resistant container.

B. Description of How the Drug Product is Intended to be Used

1. Recommended dose to the amount of drug product supplied: The drug product is supplied in bottles of 100 and 500 capsules of 50 mg/300 mg/40 mg.

2. Dosing schedule: one or 2 capsules every 4 hours as needed. Total daily dosage should not exceed 6 capsules. Extended and repeated use of this product is not recommended because of the potential for physical dependence.

C. Basis for Approvability or Not-Approval Recommendation

The Application is Approvable for the following reasons:

Chemistry: Satisfactory per L. Tang on 9-17-09
Labeling: Satisfactory per C. Park reviewed on 10-9-08
Bioequivalence: Satisfactory per P. Nwakama reviewed on 2-28-2008.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE

S.1 General Information

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

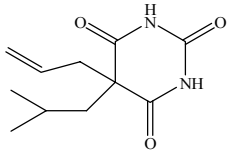
S.1.1 Nomenclature

Chemical Name:

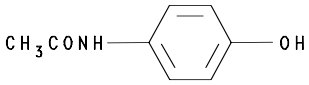
Butalbital USP: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen USP: N-(4-hydroxyphenyl)-Acetamide (b) (4)
Caffeine USP: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione (b) (4).

S.1.2 Structure

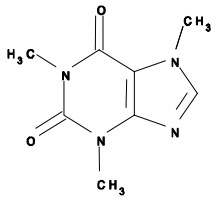
Generic name: Butalbital USP
Chemical name: 5-(2-Methylpropyl)-5-(2-propenyl)-2,4,6(1*H*, 3*H*, 5*H*)-pyrimidinetrione
Synonym: 5-allyl-5-isobutylbarbituric acid
Formula: $C_{11}H_{16}N_2O_3$
Molecular weight: (b) (4)
CAS registry number: 77-26-9
Pharmacologic and/or therapeutic category: Analgesics
Chemical structure:



Acetaminophen. USP
Chemical name (USP): Acetamide, N-(4-hydrpxyphenyl)-4”-Hydroxyacetanilide
IUPAC: N-(-hydroxyphenyl)acetamide
Formula: $C_8H_9NO_2$
Molecular weight: 151.17
CAS registry number: 103-90-2
Chemical Structure:



Caffeine USP
Chemical name: 1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-
Formula: $C_8H_{10}N_4O_2$
Molecular weight: 194.2
CAS registry number: 58-08-2
Chemical structure:



S 1.3 General Properties

Butalbital USP
Chemical name: 5-(2-Methylpropyl)-5-(2-propenyl)-2,4,6(1*H*, 3*H*, 5*H*)-pyrimidinetrione
Synonym: 5-allyl-5-isobutylbarbituric acid
Formula: $C_{11}H_{16}N_2O_3$
Molecular weight: (b) (4)
CAS registry number: 77-26-9
Pharmacologic and/or therapeutic category: Analgesics
Physical Description:

Butalbital USP is a white, crystalline powder; solubility in water is 1700 mg/L; soluble in alcohol, chloroform, ether, acetone, glacial acetic acid; also in solution of fixed alkali hydroxides.

Polymorphism: There are no known ordinarily occurring polymorphs for this substance.
pKa; N/A
Calculated dose solubility volume:

50 mg (highest strength) (solubility = 1.7 mg/mL) = 29.41 mL < 250 mL. Therefore, Butalbital is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Melting Point: (b) (4)

Log P/Hydrophobicity: 1.429

Acetaminophen. USP

Chemical name (USP): Acetamide, N-(4-hydroxyphenyl)-4'-Hydroxyacetanilide

IUPAC: N-(-hydroxyphenyl)acetamide

Formula: $C_8H_9NO_2$

Molecular weight: 151.17

CAS registry number: 103-90-2

Physical Description: Acetaminophen is a white, crystalline stable solid, solubility in water is 0.014 mg/mL (very slightly soluble in cold water; considerably more soluble in hot water)

Polymorphism: There are no known ordinarily occurring polymorphs for this substance.

pKa; 9.38

Calculated dose solubility volume:

300 mg (highest strength)/14 (lowest solubility in mg/mL @ 25º C) = 21.4 mL < 250 mL. Therefore, Acetaminophen is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Melting Point: 169 – 170.5ºC

Log P/Hydrophobicity: 0.917

Caffeine USP

Chemical name: 1,3,7-trimethylxanithine

CAS registry number: 58-08-2

Formula: $C_8H_{10}N_4O_2$

Molecular weight: 194.2

Physical Description: Caffeine is an odorless, white needles or powder, slightly soluble in water, soluble in ethyl acetate, chloroform, pyridine, pyrrole, tetrahydrofuran solution; moderately soluble in alcohol, acetone; slightly soluble in petroleum ether, ether, benzene.

Polymorphism: There are no known ordinarily occurring polymorphs for this substance.

pKa; 10.4

Calculated dose solubility volume:

40 mg (highest strength) (22 mg/mL) = 1.82 mL < 250 mL. Therefore , Caffeine is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Melting Point: 238ºC

Log P/Hydrophobicity: 0.07

S.2 Manufacture

S.2.1 Manufacturers

The manufacturers of the drug substances, Butalbital USP, Acetaminophen USP and Caffeine USP are as follows:

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

The Letters of Authorization to refer to DMFs (b) (4) are provided.
The updated (b) (4) ***was reviewed by L. Tang on 7-28-09 and found satisfactory.***
The updated (b) (4) ***was reviewed by S. Bain on 7-7-09 and found satisfactory.***
The (b) (4) ***was reviewed by R. Powers on 7-22-09 and found satisfactory.***

S.2.2 Description of Manufacturing Process and Process Controls

Refer to (b) (4) the DMFs are adequate

S.2.3 Control of Materials

Refer to (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

Refer to (b) (4)

S.2.5 Process Validation and/or Evaluation

Refer to (b) (4)

S.2.6 Manufacturing Process Development

Refer to (b) (4)

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

Refer to (b) (4)

S.3.2 Impurities

Refer to (b) (4)

S.4 Control of Drug Substance [name, manufacturer]

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

S.4.1 Specification: Satisfactory

Butalbital, USP

The firm's tests and specifications are as follows for Butalbital, USP:

(b) (4)

Chemistry comments to be provided to the Applicant

ANDA: 40-885 APPLICANT: Nexgen Pharma, Inc.

DRUG PRODUCT: Butalbital, Acetaminophen, and Caffeine Capsules, USP 50 mg/300 mg/40 mg

cc: ANDA 40-885
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/L. Tang/9-18-09

HFD-647/U. Venkataram/9-18-2009

HFD-647/S. Eng/9-22-09

40885N03_RLT/Flash card LCT #E

V:\Division of Chemistry II\Team 8\Final version for DFS\40885_N03_RLT.DOC

TYPE OF LETTER: APPROVAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-40885	ORIG-1	ANABOLIC LABORATORIES INC	BUTALBITAL;ACETAMINOPHEN;CAFFEINE
ANDA-40885	ORIG-1	ANABOLIC LABORATORIES INC	BUTALBITAL;ACETAMINOPHEN;CAFFEINE
ANDA-40885	ORIG-1	ANABOLIC LABORATORIES INC	BUTALBITAL;ACETAMINOPHEN;CAFFEINE
ANDA-40885	ORIG-1	ANABOLIC LABORATORIES INC	BUTALBITAL;ACETAMINOPHEN;CAFFEINE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUCIA C TANG
09/22/2009

UBRANI V VENKATARAM
09/23/2009

SIMON S ENG
09/23/2009

ANDA 40-885

Butalbital, Acetaminophen, and Caffeine Capsules USP,
50 mg/300 mg/40 mg

Nexgen Pharma, Inc.

Lucia C. Tang
OGD, DC II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 40-885

2. REVIEW # 2

3. REVIEW DATE: 12-3-08

4. REVIEWER: Lucia C. Tang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm:	
Original Submission	4-20-07
Communication and Correspondence	7-10-07
Acceptable for filing	4-23-07
FDA	
Acknowledgment	7-13-07
1st NA letter	3-6-08

6. SUBMISSION(S) BEING REVIEWED:

Source	Submission(s) Reviewed	Document Date
Firm:	Amendment	MAY 23, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Nexgen Pharma, Inc.
Address:	17802 Gillette Avenue Irvine, CA 92614-6502 Attention: Robert van Osdel
Representative:	Robert van Osdel
Telephone:	949 260-3704
Facsimile:	949 261-2787

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Butalbital, Acetaminophen, and Caffeine Capsules

9. LEGAL BASIS FOR SUBMISSION:

The reference listed Acetaminophen, Butalbital, and Caffeine Capsules USP, 325 mg/50 mg/ 40 mg was approved for Mikart, Inc. on March 17, 1986 (ANDA # 89007).

10. PHARMACOL. CATEGORY : Analgesic/Sedative
Relief of the symptom complex of tension headache

11. DOSAGE FORM: Hard Gel Capsules

12. STRENGTH/POTENCY: 50 mg/300 mg/40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen: N-(4-hydroxyphenyl)-Acetamide (b) (4)

Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione
(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	2-11-08	L. Tang
	II			3	Adequate	2-5-08	M. PineiroSanchez
	II			3	Adequate	5-10-07	K. Furnkranz
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION N`UMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	***Acceptable***	***11-10-08***	***OC***
Methods Validation	N/A per OGD policy		
Labeling	***Satisfactory***	***10-9-08***	***C. Park***
Bioequivalence	***Satisfactory***	***2-28-08***	***P. Nwakama***
EA	Exclusion under 21 CFR 25.31(a)		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ___ No If no, explain reason(s) below:

Executive Summary Section

The Chemistry Review for ANDA 40-885

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Application is not approvable for the following reasons:

Chemistry: Not Approvable, Minor
Labeling: Satisfactory per C. Park reviewed on 10-9-08
Bioequivalence: Satisfactory per P. Nwakama reviewed on 2-28-2008.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:+

Chemical names:
Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen: N-(4-hydroxyphenyl)-Acetamide (b) (4))

Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione (b) (4)

Drug substance Butalbital USP is a White, odorless, crystalline powder . The melting point is (b) (4)

Acetaminophen USP is a White, odorless, free-flowing granular powder, having a slightly bitter taste. (b) (4).

Caffeine USP is a White powder or white glistening needles, (b) (4), is odorless and has a bitter taste. (b) (4)

Drug Product: Butalbital, Acetaminophen, and Caffeine Capsules, USP, 50 mg/300 mg/40 mg
Description: #0 gelatin capsule, green cap, yellow body, filled with white powder

The manufacture of Butalbital, Acetaminophen, and Caffeine Capsules, USP

(b) (4)

Packaging: Butalbital, Acetaminophen, and Caffeine Capsules, USP, 50mg/300mg/40mg is packaged in 100's and 500's packaged sizes

Store at 20 to 25ºC (68 to 77ºC) [see USP Controlled Room Temperature] Dispense in a tight, light-resistant container.

B. Description of How the Drug Product is Intended to be Used

1. Recommended dose to the amount of drug product supplied: The drug product is supplied in bottles of 100 and 500 capsules of 50 mg/300 mg/40 mg.

2. Dosing schedule: one or 2 capsules every 4 hours as needed. Total daily dosage should not exceed 6 capsules. Extended and repeated use of this product is not recommended because of the potential for physical dependence.

C. Basis for Approvability or Not-Approval Recommendation

The Application is not Approvable for the following reasons:

Chemistry: Not Approvable, Minor
Labeling: Satisfactory per C. Park reviewed on 10-9-08
Bioequivalence: Satisfactory per P. Nwakama reviewed on 2-28-2008.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE

S.1 General Information

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

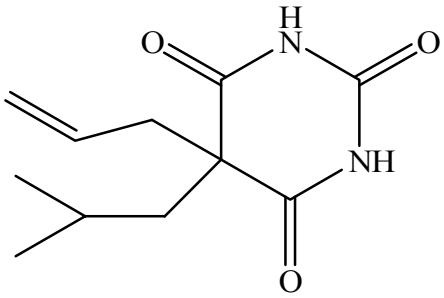
S.1.1 Nomenclature

Chemical Name:

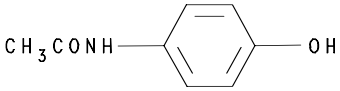
Butalbital USP: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen USP: N-(4-hydroxyphenyl)-Acetamide (b) (4)
Caffeine USP: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione (b) (4).

S.1.2 Structure

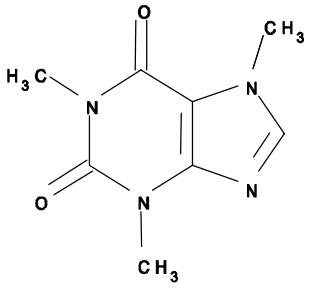
Generic name: Butalbital USP
Chemical name: 5-(2-Methylpropyl)-5-(2-propenyl)-2,4,6(1*H*, 3*H*, 5*H*)-pyrimidinetrione
Synonym: 5-allyl-5-isobutylbarbituric acid
Formula: $C_{11}H_{16}N_2O_3$
Molecular weight: (b) (4)
CAS registry number: 77-26-9
Pharmacologic and/or therapeutic category: Analgesics
Chemical structure:



Acetaminophen. USP
Chemical name (USP): Acetamide, N-(4-hydrpxyphenyl)-4”-Hydroxyacetanilide
IUPAC: N-(-hydroxyphenyl)acetamide
Formula: $C_8H_9NO_2$
Molecular weight: 151.17
CAS registry number: 103-90-2
Chemical Structure:



Caffeine USP
Chemical name: 1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-
Formula: $C_8H_{10}N_4O_2$
Molecular weight: 194.2
CAS registry number: 58-08-2
Chemical structure:



S 1.3 General Properties

Butalbital USP
Chemical name: 5-(2-Methylpropyl)-5-(2-propenyl)-2,4,6(1*H*, 3*H*, 5*H*)-pyrimidinetrione
Synonym: 5-allyl-5-isobutylbarbituric acid
Formula: $C_{11}H_{16}N_2O_3$

Molecular weight: (b) (4)
CAS registry number: 77-26-9
Pharmacologic and/or therapeutic category: Analgesics
Physical Description:

Butalbital USP is a white, crystalline powder; solubility in water is 1700 mg/L; soluble in alcohol, chloroform, ether, acetone, glacial acetic acid; also in solution of fixed alkali hydroxides.

Polymorphism: There are no known ordinarily occurring polymorphs for this substance.
pKa; N/A
Calculated dose solubility volume:

50 mg (highest strength) (solubility = 1.7 mg/mL) = 29.41 mL < 250 mL. Therefore, Butalbital is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Melting Point: (b) (4)
Log P/Hydrophobicity: 1.429

Acetaminophen. USP
Chemical name (USP): Acetamide, N-(4-hydroxyphenyl)-4'-Hydroxyacetanilide
IUPAC: N-(-hydroxyphenyl)acetamide
Formula: $C_8H_9NO_2$
Molecular weight: 151.17
CAS registry number: 103-90-2
Physical Description: Acetaminophen is a white, crystalline stable solid, solubility in water is 0.014 mg/mL (very slightly soluble in cold water; considerably more soluble in hot water)
Polymorphism: There are no known ordinarily occurring polymorphs for this substance.
pKa; 9.38
Calculated dose solubility volume:

(b) (4)

Calculated dose solubility volume: 300 mg (highest strength)/14 (lowest solubility in mg/mL @ 25º C) = 21.4 mL < 250 mL. Therefore, Acetaminophen is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Melting Point: 169 – 170.5ºC
Log P/Hydrophobicity: 0.917

Comments from CR#1:

Q:1. Regarding the drug substance:

Q:1.a. We note that calculated dose solubility volume for Acetaminophen in general information section is an error. Please revise and resubmit it.

A: OK (see response 1.a and Attachment 1 of May 23, 2008 amendment). Copies of each revised page for Module 2 (QOS) and Module 3 Section 3.2.SA

with revised dose/solubility volume calculation for Acetaminophen shown in Attachment l has been reviewed and found acceptable. Calculated dose solubility volume: 300 mg (highest strength)/14 (lowest solubility in mg/mL @ 25º C) = 21.4 mL < 250 mL. Therefore, Acetaminophen is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Caffeine USP
Chemical name: 1,3,7-trimethylxanithine
CAS registry number: 58-08-2
Formula: $C_8H_{10}N_4O_2$
Molecular weight: 194.2
Physical Description: Caffeine is an odorless, white needles or powder, slightly soluble in water, soluble in ethyl acetate, chloroform, pyridine, pyrrole, tetrahydrofuran solution; moderately soluble in alcohol, acetone; slightly soluble in petroleum ether, ether, benzene.
Polymorphism: There are no known ordinarily occurring polymorphs for this substance.
pKa; 10.4
Calculated dose solubility volume:
40 mg (highest strength) (22 mg/mL) = 1.82 mL < 250 mL. Therefore , Caffeine is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)
Melting Point: 238ºC
Log P/Hydrophobicity: 0.07

S.2 Manufacture

S.2.1 Manufacturers

The manufacturers of the drug substances, Butalbital USP, Acetaminophen USP and Caffeine USP are as follows:

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

The Letters of Authorization to refer to [redacted] are provided.

The [redacted] was reviewed by S. Bain on 6-29-07 and found satisfactory. However,
FDA Comments regarding [redacted] on 6-29-07as follows:
Please provide a Summary and Annotation of Changes Section in the future updates of this and other DMFS.
Firm Response on August 30, 2007:
They will comply with your request to provide a Summary and Annotation of Changes Section in the future updates of all of their DMFs.
The updated [redacted] was reviewed by L. Tang on 2-11-08 and found satisfactory.
The updated [redacted] was reviewed by M. Pineiro Sanchez on 2-5-08 and found satisfactory.
The [redacted] was reviewed by K Furnkranz on 5-10-07 and found satisfactory. There is no updated information except an authorization letter submitted dated on September 25, 2007

S.2.2 Description of Manufacturing Process and Process Controls

Refer to [redacted] the DMFs are adequate

S.2.3 Control of Materials

Refer to [redacted]

S.2.4 Controls of Critical Steps and Intermediates

Refer to [redacted]

S.2.5 Process Validation and/or Evaluation

Refer to [redacted]

S.2.6 Manufacturing Process Development

Refer to [redacted]

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

Refer to [redacted]

S.3.2 Impurities

Refer to [redacted]

S.4 Control of Drug Substance [name, manufacturer]

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

S.4.1 Specification: Satisfactory

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please submit all available stability data

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-885
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/L. Tang/12-3-08, revised 12-11-2008

HFD-647/U. Venkataram/12-04-2008; 11-Dec-2008

HFD-647/N. Patel/12-22-08

40885N02_RLT/Flash card LCT #E

V:\Division of Chemistry II\Team 8\Final version for DFS\40885N02_RLT.DOC

TYPE OF LETTER: NOT APPROVABLE – MINOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lucia C. Tang
12/22/2008 11:21:55 AM
CHEMIST

Ubrani Venkataram
12/22/2008 02:58:26 PM
CHEMIST

Nitin Patel
12/23/2008 10:46:12 AM
CSO

ANDA 40-885

Butalbital, Acetaminophen, and Caffeine Capsules USP,
50 mg/300 mg/40 mg

Nexgen Pharma, Inc.

Lucia C. Tang
OGD, DC II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 40-885

2. REVIEW # 1

3. REVIEW DATE: 2-22-08

4. REVIEWER: Lucia C. Tang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

SUBMISSION(S) BEING REVIEWED:

Source	Submission(s) Reviewed	Document Date
Firm	Original Submission Communication and Correspondence	4-20-07 7-10-07

7. NAME & ADDRESS OF APPLICANT:

Name:	Nexgen Pharma, Inc.
Address:	17802 Gillette Avenue Irvine, CA 92614-6502 Attention: Robert van Osdel
Representative:	Robert van Osdel
Telephone:	949 260-3704
Facsimile:	949 261-2787

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Butalbital, Acetaminophen, and Caffeine Capsules

9. LEGAL BASIS FOR SUBMISSION:

The reference listed Acetaminophen, Butalbital, and Caffeine Capsules USP, 325 mg/50 mg/ 40 mg was approved for Mikart, Inc. on March 17, 1986 (ANDA # 89007).

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY : Analgesic/Sedative
Relief of the symptom complex of tension headache

11. DOSAGE FORM: Hard Gel Capsules

12. STRENGTH/POTENCY: 50 mg/300 mg/40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen: N-(4-hydroxyphenyl)-Acetamide (b) (4)

Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione (b) (4).

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	2-11-08	L. Tang
	II			3	Adequate	2-5-08	M. PineiroSanchez
	II			3	Adequate	5-10-07	K. Furnkranz
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION N`UMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A per OGD policy		
Labeling	Not Satisfactory	8-6-07	C. Park
Bioequivalence	Not Satisfactory	11-21-07	P. Nwakama
EA	Exclusion under 21 CFR 25.31(a)		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.

__X__ Yes ___ No If no, explain reason(s) below:

Executive Summary Section

The Chemistry Review for ANDA 40-885

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Application is not approvable for the following reasons:

Chemistry: Not Approvable, Minor
Labeling: Not Satisfactory per C. Park reviewed on 8-6-07
Bioequivalence: Not Satisfactory per P. Nwakama reviewed on 11-21-2007.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:

Chemical names:
Butalbital: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen: N-(4-hydroxyphenyl)-Acetamide (b) (4)

Caffeine: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione (b) (4)).

Drug substance Butalbital USP is a White, odorless, crystalline powder . The melting point is (b) (4)

Acetaminophen USP is a White, odorless, free-flowing granular powder, having a slightly bitter taste. (b) (4)

Caffeine USP is a White powder or white glistening needles. (b) (4) is odorless and has a bitter taste. (b) (4)

Drug Product: Butalbital, Acetaminophen, and Caffeine Capsules, USP, 50 mg/300 mg/40 mg
Description: #0 gelatin capsule, green cap, yellow body, filled with white powder

The manufacture of Butalbital, Acetaminophen, and Caffeine Capsules, USP

(b) (4)

Packaging: Butalbital, Acetaminophen, and Caffeine Capsules, USP, 50mg/300mg/40mg is packaged in 100's and 500's packaged sizes

Store and Dispense (Not Satisfactory): The following statement is requested by Labeling reviewer
Store at 20 to 25ºC (68 to 77ºC) [see USP Controlled Room Temperature] Dispense in a tight, light-resistant container.

B. Description of How the Drug Product is Intended to be Used

1. Recommended dose to the amount of drug product supplied: The drug product is supplied in bottles of 100 and 500 capsules of 50 mg/300 mg/40 mg.

2. Dosing schedule: one or 2 capsules every 4 hours as needed. Total daily dosage should not exceed 6 capsules. Extended and repeated use of this product is not recommended because of the potential for physical dependence.

C. Basis for Approvability or Not-Approval Recommendation

The Application is not Approvable for the following reasons:

Chemistry: Not Approvable, Minor
Labeling: Not Satisfactory per A. Vezza reviewed on 1-24-08
Bioequivalence: Not Satisfactory per B. Li reviewed on 11-27-2007.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE

S.1 General Information

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

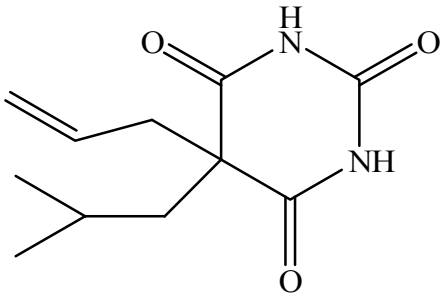
S.1.1 Nomenclature

Chemical Name:

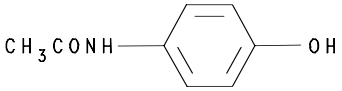
Butalbital USP: 5-Allyl-5-isobutylbarbituric acid ($C_{11}H_{16}N_2O_3$)
Acetaminophen USP: N-(4-hydroxyphenyl)-Acetamide (b) (4)
Caffeine USP: 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione (b) (4)

S.1.2 Structure

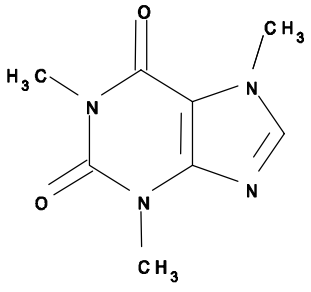
Generic name: Butalbital USP
Chemical name: 5-(2-Methylpropyl)-5-(2-propenyl)-2,4,6(1*H*, 3*H*, 5*H*)-pyrimidinetrione
Synonym: 5-allyl-5-isobutylbarbituric acid
Formula: $C_{11}H_{16}N_2O_3$
Molecular weight: (b) (4)
CAS registry number: 77-26-9
Pharmacologic and/or therapeutic category: Analgesics
Chemical structure:



Acetaminophen. USP
Chemical name (USP): Acetamide, N-(4-hydrpxyphenyl)-4”-Hydroxyacetanilide
IUPAC: N-(-hydroxyphenyl)acetamide
Formula: $C_8H_9NO_2$
Molecular weight: 151.17
CAS registry number: 103-90-2
Chemical Structure:



Caffeine USP
Chemical name: 1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-
Formula: $C_8H_{10}N_4O_2$
Molecular weight: 194.2
CAS registry number: 58-08-2
Chemical structure:



S 1.3 General Properties

Butalbital USP
Chemical name: 5-(2-Methylpropyl)-5-(2-propenyl)-2,4,6(1*H*, 3*H*, 5*H*)-pyrimidinetrione
Synonym: 5-allyl-5-isobutylbarbituric acid
Formula: $C_{11}H_{16}N_2O_3$

Molecular weight: (b) (4)
CAS registry number: 77-26-9
Pharmacologic and/or therapeutic category: Analgesics
Physical Description:

Butalbital USP is a white, crystalline powder; solubility in water is 1700 mg/L; soluble in alcohol, chloroform, ether, acetone, glacial acetic acid; also in solution of fixed alkali hydroxides.

Polymorphism: There are no known ordinarily occurring polymorphs for this substance.
pKa; N/A
Calculated dose solubility volume:

50 mg (highest strength) (solubility = 1.7 mg/mL) = 29.41 mL < 250 mL. Therefore, Butalbital is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Melting Point: (b) (4)
Log P/Hydrophobicity: 1.429

Acetaminophen. USP
Chemical name (USP): Acetamide, N-(4-hydroxyphenyl)-4'-Hydroxyacetanilide
IUPAC: N-(-hydroxyphenyl)acetamide
Formula: $C_8H_9NO_2$
Molecular weight: 151.17
CAS registry number: 103-90-2
Physical Description: Acetaminophen is a white, crystalline stable solid, solubility in water is 0.014 mg/mL (very slightly soluble in cold water; considerably more soluble in hot water)
Polymorphism: There are no known ordinarily occurring polymorphs for this substance.
pKa; 9.38
Calculated dose solubility volume:

(b) (4)

Melting Point: 169 – 170.5ºC
Log P/Hydrophobicity: 0.917

Comments:

We note that calculated dose solubility volume for Acetaminophen in general information section is in error. Please revise and resubmit it.

Caffeine USP
Chemical name: 1,3,7-trimethylxanithine
CAS registry number: 58-08-2
Formula: $C_8H_{10}N_4O_2$
Molecular weight: 194.2
Physical Description: Caffeine is an odorless, white needles or powder, slightly soluble in water, soluble in ethyl acetate, chloroform, pyridine, pyrrole,

tetrahydrofuran solution; moderately soluble in alcohol, acetone; slightly soluble in petroleum ether, ether, benzene.

Polymorphism: There are no known ordinarily occurring polymorphs for this substance.

pKa; 10.4

Calculated dose solubility volume:

40 mg (highest strength) (22 mg/mL) = 1.82 mL < 250 mL. Therefore , Caffeine is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS)

Melting Point: 238°C

Log P/Hydrophobicity: 0.07

S.2 Manufacture

S.2.1 Manufacturers

The manufacturers of the drug substances, Butalbital USP, Acetaminophen USP and Caffeine USP are as follows:

Name: Butalbital USP
Manufacturer: (b) (4)

Name: Acetaminophen USP
Manufacturer: (b) (4)

Name: Caffeine USP
Manufacturer: (b) (4)

The Letters of Authorization to refer to (b) (4) are provided.

The (b) (4) was reviewed by S. Bain on 6-29-07 and found satisfactory. However,

FDA Comments regarding (b) (4) on 6-29-07as follows:

Please provide a Summary and Annotation of Changes Section in the future updates of this and other DMFS.

Firm Response on August 30, 2007:

They will comply with your request to provide a Summary and Annotation of Changes Section in the future updates of all of their DMFs.

The updated (b) (4) was reviewed by L. Tang on 2-11-08 and found satisfactory.

The updated (b) (4) was reviewed by M. Pineiro Sanchez on 2-5-08 and found satisfactory.

The [redacted] was reviewed by K Furnkranz on 5-10-07 and found satisfactory. There is no updated information except an authorization letter submitted dated on September 25, 2007

S.2.2 Description of Manufacturing Process and Process Controls

Refer to [redacted]

S.2.3 Control of Materials

Refer to [redacted]

S.2.4 Controls of Critical Steps and Intermediates

Refer to [redacted]

S.2.5 Process Validation and/or Evaluation

Refer to [redacted]

S.2.6 Manufacturing Process Development

Refer to [redacted]

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

Refer to [redacted]

S.3.2 Impurities

Refer to [redacted]

S.4 Control of Drug Substance [name, manufacturer]

Name: Butalbital USP
Manufacturer: [redacted]

Name: Acetaminophen USP
Manufacturer: [redacted]

Name: Caffeine USP
Manufacturer: [redacted]

(b) (4)

S.4.1 Specification: Not satisfactory

(b) (4)

nt,

28 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

cc: ANDA 40-885
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-647/L. Tang/2-22-08, revised 3-3-08

HFD-647/U. Venkataram/28-Feb-2008; 04-Mar-2008

HFD-647/N. Patel/04-Mar-2008

F/T by np

40885N01_RLT/disk LCT D#4

V:\Division of Chemistry II\Team 8\Final version for DFS\40885N01_RLT.DOC

TYPE OF LETTER: NOT APPROVABLE – MINOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lucia C. Tang
3/4/2008 05:00:44 PM
CHEMIST

Ubrani Venkataram
3/5/2008 01:00:04 PM
CHEMIST

Nitin Patel
3/5/2008 02:44:18 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040885

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	40-885
Drug Product Name	Butalbital, Acetaminophen & Caffeine Capsules USP
Strength(s)	50 mg/300 mg/40 mg
Applicant Name	Anabolic Laboratories, Inc.
Address	17802 Gillette Avenue, Irvine, CA 92614-6502
Applicant's Point of Contact	Robert van Osdel
Contact's Telephone Number	949-260-3704
Contact's Fax Number	949-261-2787
Original Submission Date(s)	03/20/2007
Submission Date(s) of Amendment(s) Under Review	December 3, 2007
Reviewer	Patrick Nwakama, Pharm.D.
OUTCOME DECISION	**ACCEPTABLE**

1 EXECUTIVE SUMMARY

This is a review of the dissolution amendment and waiver request.

There is a USP method for this product. However, the firm originally submitted dissolution testing data using a dissolution method different from that of the USP. The dissolution testing was found incomplete and the firm was requested to repeat dissolution testing using the USP method.

In the current submission, the firm has submitted dissolution data using the USP method. The dissolution testing is acceptable.

The waiver request of in vivo bioequivalence study requirements is granted per 21 CFR 320.22(c).

The application is acceptable.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Acetaminophen, Butalbital & Caffeine Capsules, USP, 300 mg/50 mg/40 mg
Reference Product	Acetaminophen, Butalbital & Caffeine Capsules, USP, 325 mg/50 mg/40 mg
RLD Manufacturer	MIKART
NDA No.	089007
RLD Approval Date	Mar 17, 1986
Indication	Treatment of tension headaches, migraines, and mild to moderate pain, especially when anti-anxiety or relaxant effects are needed

3.2 OGD Recommendations for Drug Product

Source of most recent recommendations:	OGD #07-0235; Hetero; 1/30/2007
Summary of OGD or DBE History (for details, see Appendix 4.4):	There is no recommendation found for the capsule dosage form of this combination product. For the tablet dosage from, the OGD provided the following BE recommendations: 1. The following study is recommended to establish bioequivalence of Acetaminophen; Butalbital; Caffeine Tablets: A single-dose fasting in-vivo bioequivalence study comparing Acetaminophen; Butalbital; Caffeine Tablets, 500 mg; 50 mg; 40 mg, to the RLD, Esgic-Plus® (Acetaminophen; Butalbital; Caffeine) Tablets, 500 mg; 50 mg; 40 mg. 2. Please measure only the parent compound, Butalbital. 3. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method.

3.3 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	Yes	1
Waiver requests	Yes	1
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

3.4 Review of Submission (Response to DBE Deficiency Letter dated 11/21/2007)

DEFICIENCY COMMENT #1:
Your proposed dissolution method (900 mL, Water, (b) (4) is not acceptable. Please repeat your dissolution testing using the current USP method:

Apparatus:	I (Basket)
Speed of Rotation:	100 rpm
Medium:	Water
Volume:	900 mL; 37°C
Specifications	NLT 80% *(Q)* in 60 minutes for all 3 components

FIRM'S RESPONSE:
The firm has submitted dissolution method using the above USP method.

DBE COMMENT:
The results of the dissolution testing are acceptable.

3.5 Formulation

Location in appendix	Section 4.1, Page 6
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

3.6 In Vitro Dissolution

Location of DBE Dissolution Review	Section 4.2, Page 7
Source of Method (USP, FDA or Firm)	USP
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	I (Basket)
Rotation (rpm)	100 rpm
DBE-recommended specifications	NLT 80% (Q) in 60 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	N/A
If no, reason why F2 not calculated	N/A
Is method acceptable?	Yes
If not then why?	N/A

3.7 Waiver Request(s)

Strengths for which waivers are requested	50 mg/300 mg/40 mg
Regulation cited	21 CFR 320.22(c)
Proportional to strength tested in vivo?	NA
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	N/A

3.8 Deficiency Comments

None.

3.9 Recommendations

1. The dissolution testing conducted by Anabolic Laboratories, Inc. on the test product, Butalbital, Acetaminophen & Caffeine Tablets USP, 50 mg /300 mg/40 mg (lot # 318500) is acceptable. The DBE acknowledges that the firm will follow the USP method and specification for this drug product.

2. The application is complete. Waiver of in vivo bioequivalence testing requirements for Butalbital, Acetaminophen & Caffeine Tablets USP, 50 mg /300 mg/40 mg is granted.

3.10 Comments for Other OGD Disciplines

Discipline	Comment
None	

4 APPENDIX

4.1 Formulation Data

Component	Component	Amount (mg) per Capsule
Active Ingredients	Butalbital, USP	50.0
	Acetaminophen, USP	300.0
	Caffeine, USP (anhydrous)	40.0
Inactive Ingredients	Sodium Lauryl Sulfate, NF	(b) (4)
	Talc, USP	
	Stearic Acid, NF	
	Microcrystalline Cellulose, NF	
Core Weight		
#0 Hard Gelatin Capsule	(b) (4)	
Total Weight		**704.0**

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	All the inactive ingredients are within the current IIG

4.2 Dissolution Data

Dissolution Review Path	N/A

Table 1. Dissolution Data

Dissolution Conditions	**Apparatus:**	I (Basket)
	Speed of Rotation:	100 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37°C
Firm's Proposed Specifications	NLT 80% *(Q)* in 60 minutes for all three components	
Dissolution Testing Site (Name, Address)		

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 10 min	20 min	30 min	45 min	60 min	Study Report Location
Study Report 154/60-77		Test Product **Butalbital**	50 mg Tablet	12	Mean	75.9	92.7	97.5	99.1	99.7	Vol. 1.1 Section 5.3.1.2
					Range	(b) (4)					
					%CV	8.7	4.2	2.5	1.8	1.4	
Study Report 154/185-207		Reference Product **Butalbital**	50 mg Tablet	12	Mean	56.4	90.1	97.8	99.4	100.0	
					Range	(b) (4)					
					%CV	13.6	6.1	3.0	2.2	2.3	
Study Report 154/60-77		Test Product **Acetaminophen**	300 mg Tablet	12	Mean	76.9	97.0	101.1	102.3	102.2	
					Range	(b) (4)					
					%CV	8.0	3.8	2.1	1.9	1.7	
Study Report 154/185-207		Reference Product **Acetaminophen**	**325** mg Tablet	12	Mean	57.9	90.7	98.2	99.3	99.8	
					Range	(b) (4)					
					%CV	12.5	5.9	2.8	1.9	2.0	
Study Report 154/60-77		Test Product **Caffeine**	40 mg Tablet	12	Mean	78.3	95.5	99.3	99.9	100.0	
					Range	(b) (4)					
					%CV	12.7	5.0	2.4	1.5	1.5	
Study Report 154/185-207		Reference Product **Caffeine**	40 mg Tablet	12	Mean	51.1	91.9	97.4	98.3	98.7	
					Range	(b) (4)					
					%CV	13.3	5.7	3.0	2.5	2.7	

BIOEQUIVALENCE COMMNENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40885

APPLICANT: Anabolic Laboratories, Inc.

DRUG PRODUCT: Butalbital, Acetaminophen & Caffeine Capsules USP, 50 mg/300 mg/40 mg

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

We acknowledge that you have accepted the dissolution method and specification as specified in the USP for this drug product.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

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

4.3 Outcome Page

ANDA: 40-885

COMPLETED ASSIGNMENT FOR 40885 ID: 4731

Reviewer: Nwakama, Patrick **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4731	12/3/2007	Other	Dissolution Amendment	1	1
				Bean Total:	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patrick E. Nwakama
2/25/2008 02:56:24 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
2/27/2008 06:32:14 AM

Barbara Davit
2/28/2008 03:51:43 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-885
Drug Product Name	Butalbital, Acetaminophen & Caffeine Capsules USP
Strength(s)	50 mg/300 mg/40 mg
Applicant Name	Anabolic Laboratories, Inc.
Address	17802 Gillette Avenue, Irvine, CA 92614-6502
Applicant's Point of Contact	Robert van Osdel
Contact's Telephone Number	949-260-3704
Contact's Fax Number	949-261-2787
Original Submission Date(s)	03/20/2007
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Patrick Nwakama, Pharm.D.
OUTCOME DECISION	**INCOMPLETE**

1 EXECUTIVE SUMMARY

This is a review of the dissolution testing data and a waiver request.

The reference drug product, Esgic® Capsules is rated AB in the Orange Book. The Agency approved (3/31/2005) a Citizen Petition (FDA's Docket No.2004P-0561/CP) requesting permission to file an ANDA for Acetaminophen, Butalbital and Caffeine Capsules, **300** mg/50 mg/40 mg using Esgic® (Acetaminophen, Butalbital and Caffeine Capsules, **325** mg/50 mg/40 mg) Capsules as the RLD. The test product formulation is acceptable.

This drug product is the subject of a USP monograph. There is a USP method for this product. The firm submitted dissolution testing data with a dissolution method different from that of the USP. The firm should repeat dissolution testing using the USP method. The dissolution testing is incomplete.

The waiver request of in vivo bioequivalence study requirements is not granted.

The application is incomplete.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Acetaminophen, Butalbital & Caffeine Capsules, USP, 300 mg/50 mg/40 mg
Reference Product	Acetaminophen, Butalbital & Caffeine Capsules, USP, 325 mg/50 mg/40 mg
RLD Manufacturer	MIKART
NDA No.	089007
RLD Approval Date	Mar 17, 1986
Indication	Treatment of tension headaches, migraines, and mild to moderate pain, especially when anti-anxiety or relaxant effects are needed

3.2 OGD Recommendations for Drug Product

Source of most recent recommendations:	OGD #07-0235; Hetero; 1/30/2007
Summary of OGD or DBE History (for details, see Appendix 4.4):	There is no recommendation found for the capsule dosage form of this combination product. For the tablet dosage from, the OGD provided the following BE recommendations: 1. The following study is recommended to establish bioequivalence of Acetaminophen; Butalbital; Caffeine Tablets: A single-dose fasting in-vivo bioequivalence study comparing Acetaminophen; Butalbital; Caffeine Tablets, 500 mg; 50 mg; 40 mg, to the RLD, Esgic-Plus® (Acetaminophen; Butalbital; Caffeine) Tablets, 500 mg; 50 mg; 40 mg. 2. Please measure only the parent compound, Butalbital. 3. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method.

3.3 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	Yes	1
Waiver requests	Yes	1
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	No	0

3.4 Formulation

Location in appendix	Section 4.1, Page 6
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

3.5 In Vitro Dissolution

Location of DBE Dissolution Review	Section 4.2, Page 7
Source of Method (USP, FDA or Firm)	Firm
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	(b) (4)
Rotation (rpm)	Not provided
DBE-recommended specifications	N/A
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Firm did not use USP Method
Is method acceptable?	No
If not then why?	Firm did not use USP Method

3.6 Waiver Request(s)

Strengths for which waivers are requested	50 mg/300 mg/40 mg
Regulation cited	21 CFR 320.22(c)
Proportional to strength tested in vivo?	NA
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	Firm did not conduct dissolution testing using USP method.

3.7 Deficiency Comments

The dissolution testing is not acceptable. This drug product is the subject of a USP monograph. The firm did not conduct dissolution testing using USP method.

3.8 Recommendations

1. The dissolution testing conducted by Anabolic Laboratories, Inc. on the test product, Butalbital, Acetaminophen & Caffeine Tablets USP, 50 mg /300 mg/40 mg (lot # 318500) is not acceptable. The DBE acknowledges that the firm will follow the USP method and specification for this drug product.

2. The application is incomplete. Waiver of in vivo bioequivalence testing requirements for Butalbital, Acetaminophen & Caffeine Tablets USP, 50 mg /300 mg/40 mg is not granted.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
None	

4 APPENDIX

4.1 Formulation Data

Component	Component	Amount (mg) per Capsule
Active Ingredients	Butalbital, USP	50.0
	Acetaminophen, USP	300.0
	Caffeine, USP (anhydrous)	40.0
Inactive Ingredients	Sodium Lauryl Sulfate, NF	(b) (4)
	Talc, USP	
	Stearic Acid, NF	
	Microcrystalline Cellulose, NF	
Core Weight		
#0 Hard Gelatin Capsule	(b) (4)	
Total Weight		**704.0**

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	All the inactive ingredients are within the current IIG

4.2 Dissolution Data

Dissolution Review Path	N/A

Table 1. Dissolution Data

USP Method:

Apparatus:	I (Basket)
Speed of Rotation:	100 rpm
Medium:	Water
Volume:	900 mL; 37°C
Specifications	NLT 80% *(Q)* in 60 minutes for all three components

Dissolution Conditions	**Apparatus:**	(b) (4)
	Speed of Rotation:	Not Provided
	Medium:	Water
	Volume:	900 mL
	Temperature:	37° C
Firm's Proposed Specifications	Not Provided	
Dissolution Testing Site (Name, Address)		

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 10 min	20 min	30 min	45 min	60 min	Study Report Location
Study Report 154/78		Test Product **Butalbital**	50 mg Tablet	12	Mean	75.9	92.7	97.5	99.1	99.7	Vol. C1.1 Section 5.3.1
					(b) (4)						
					%CV	8.7	4.2	2.5	1.8	1.4	
Study Report 154/154		Reference Product **Butalbital**	50 mg Tablet	12	Mean	56.4	90.1	97.8	99.4	100.0	
					(b) (4)						
					%CV	13.6	6.1	3.0	2.2	2.3	
Study Report 154/78		Test Product **Acetaminophen**	300 mg Tablet	12	Mean	76.9	97.0	101.1	102.3	102.2	
					(b) (4)						
					%CV	8.0	3.8	2.1	1.9	1.7	
Study Report 154/154		Reference Product **Acetaminophen**	**325** mg Tablet	12	Mean	57.9	90.7	98.2	99.3	99.8	
					(b) (4)						
					%CV	12.5	5.9	2.8	1.9	2.0	
Study Report 154/78		Test Product **Caffeine**	40 mg Tablet	12	Mean	78.3	95.5	99.3	99.9	100.0	
					(b) (4)						
					%CV	12.7	5.0	2.4	1.5	1.5	
Study Report 154/154		Reference Product **Caffeine**	40 mg Tablet	12	Mean	51.1	91.9	97.4	98.3	98.7	
					(b) (4)						
					%CV	13.3	5.7	3.0	2.5	2.7	

Figure 1. Dissolution Profiles

Not applicable

4.3 Detailed Regulatory History (If Applicable)

Not applicable

4.4 Consult Reviews

Not applicable

4.5 Additional Attachments

Not applicable

DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 40885

APPLICANT: Anabolic Laboratories, Inc.

DRUG PRODUCT: Butalbital, Acetaminophen & Caffeine Capsules USP, 50 mg/300 mg/40 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. The following deficiency has been identified:

Your proposed dissolution method (900 mL, Water, (b) (4) is not acceptable. Please repeat your dissolution testing using the current USP method:

Apparatus:	I (Basket)
Speed of Rotation:	100 rpm
Medium:	Water
Volume:	900 mL; 37°C
Specifications	NLT 80% *(Q)* in 60 minutes for all 3 components

Sincerely yours,

{See appended electronic signature page}

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

4.6 Outcome Page

ANDA: 40-885

COMPLETED ASSIGNMENT FOR 40885 ID: 910

Reviewer: Nwakama, Patrick **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
910	3/20/2007	Other	Dissolution Waiver	1	1
910	3/20/2007	Dissolution Data	Dissolution Review	1	1
				Bean Total:	2

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/s/

Patrick E. Nwakama
11/16/2007 11:36:13 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
11/16/2007 12:02:20 PM
BIOPHARMACEUTICS

Dale Conner
11/19/2007 09:23:57 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040885

Other Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: DMETS			FROM: Chan Park, Labeling Branch, OGD	
DATE: July 19, 2007	IND NO.:	ANDA NO.: 40-885	TYPE OF DOCUMENT : Original	DATE OF DOCUMENT: April 20, 2007
NAME OF DRUG: (b) (4)	PRIORITY CONSIDERATION: N/A		CLASSIFICATION OF DRUG: Anesthetic agent	DESIRED COMPLETION DATE: Within 90 days

NAME OF FIRM: Nexgen Pharma, Inc.

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
PROGRESS REPORT
NEW CORRESPONDENCE
DRUG ADVERTISING
ADVERSE REACTION REPORT
MANUFACTURING CHANGE/ADDITION
MEETING PLANNED BY
PRE--NDA MEETING
END OF PHASE II MEETING
RESUBMISSION
SAFETY/EFFICACY
PAPER NDA
CONTROL SUPPLEMENT
RESPONSE TO DEFICIENCY LETTER
FINAL PRINTED LABELING
LABELING REVISION
ORIGINAL NEW CORRESPONDENCE
FORMULATIVE REVIEW
OTHER *(SPECIFY BELOW)*: **Proprietary Name Evaluation**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER:	CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER:

III. BIOPHARMACEUTICS

DISSOLUTION
BIOAVAILABILTY STUDIES
PHASE IV STUDIES
DEFICIENCY LETTER RESPONSE
PROTOCOL-BIOPHARMACEUTICS
IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC REACTIONS (List below)
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
Γ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIO
The sponsor proposed a proprietary name (b) (4) for Butalbital, APAP, and Caffeine Capsules USP, 50 mg/300 mg/40 mg. The RLD is Esgic Capsules (ANDA 89-007). . Please review this proposed name and forward your comments to my attention. We in OGD believe that the proposed name including the numbers may not be approved, but we will wait for your review and comments. Thank you for your help with this name review.

SIGNATURE OF REQUESTER: Chan H. Park	METHOD OF DELIVERY (Check one): Ξ E- MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

(b) (4) (butalbital, acetaminophen, and caffeine capsules, usp) Capsule [Nexgen Pharma, Inc.]

DESCRIPTION

Butalbital, Acetaminophen and Caffeine Capsules USP are supplied in hard-gelatin capsule form for oral administration.

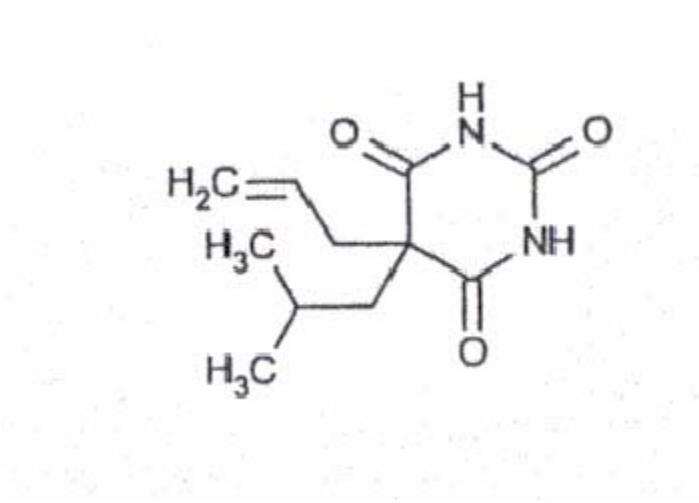
Each capsule contains the following active ingredients:

butalbital USP……50 mg
acetaminophen USP…….300 mg
caffeine USP……..40 mg

Inactive Ingredients: sodium lauryl sulfate, talc, microcrystalline cellulose, and stearic acid.

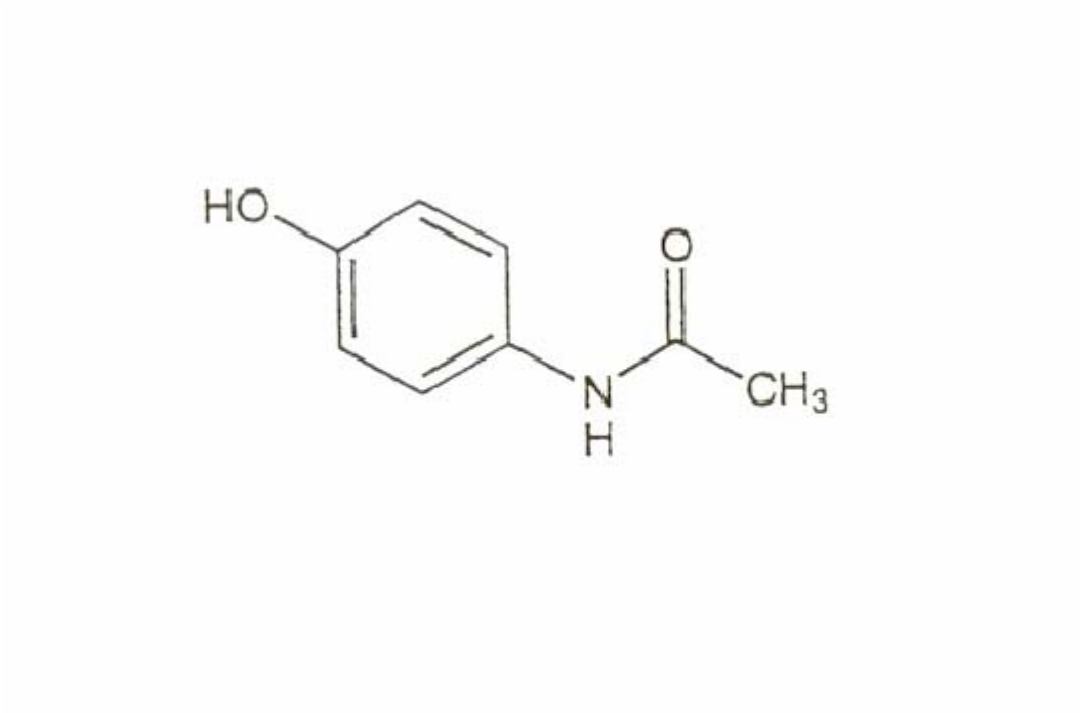
Butalbital (5-allyl-5-isobutylbarbituric acid), is a short to intermediate-acting barbiturate. It has the following structural formula:

$C_{11}H_{16}N_2O_3$ **(b) (4)**



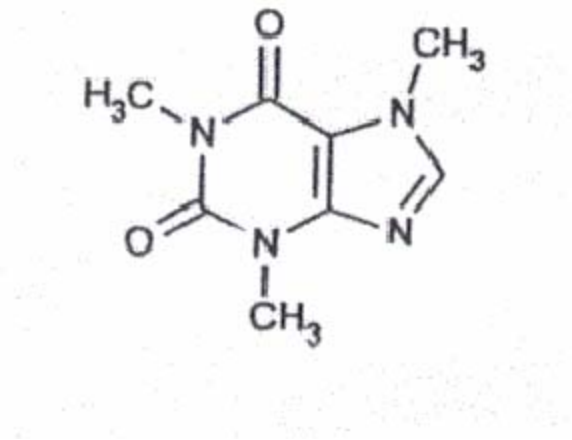
Acetaminophen (4´-hydroxyacetanilide), is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:

$C_8H_9NO_2$ **Mol. wt. 151.17**



Caffeine (1,3,7-trimethylxanthine), is a central nervous system stimulant. It has the following structural formula:

$C_8H_{10}N_4O_2$ **Mol. wt. 194.19**



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 0.5-20 mcg/mL. This falls within the range of plasma protein binding (20%-45%) reported with other barbiturates such as phenobarbital, pentobarbital, and secobarbital sodium. The plasma-to-blood concentration ratio was almost unity, indicating that there is no preferential distribution of butalbital into either plasma or blood cells.

See **OVERDOSAGE** for toxicity information.

Acetaminophen

Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following 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-methylxanthine and 1-methyluric acid. Of the 70% of the dose that is recovered in the urine, only 3% is unchanged drug.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Butalbital, Acetaminophen and Caffeine 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

Butalbital, acetaminophen, and caffeine capsules 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.

For information on use in geriatric patients, see **PRECAUTIONS/Geriatric Use**.

Laboratory Tests

In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions

The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

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

Drug/Laboratory Test Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether acetaminophen or butalbital have a potential for carcinogenesis, mutagenesis or impairment of fertility.

Pregnancy

Teratogenic Effects

Pregnancy Category C: Animal reproduction studies have not been conducted with this combination product. It is also not known whether butalbital, acetaminophen, and caffeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This product should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last two months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Nursing Mothers

Caffeine, barbiturates, and acetaminophen are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from butalbital, acetaminophen, and caffeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use

Clinical studies of butalbital, acetaminophen and caffeine capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Butalbital is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Frequently Observed

The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

Infrequently Observed

All adverse events tabulated below are classified as infrequent.

Central Nervous System: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure. Mental confusion, excitement, or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.

Autonomic Nervous System: dry mouth, hyperhidrosis.

Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain, muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.

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

The following adverse drug events may be borne in mind as potential effects of the components of this product. Potential effects of high dosage are listed in the OVERDOSAGE section.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

DRUG ABUSE AND DEPENDENCE

Abuse and Dependence

Butalbital

Barbiturates may be habit-forming: Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient’s regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE

Following an acute overdosage of butalbital, acetaminophen, and caffeine, toxicity may result from the barbiturate or the acetaminophen. Toxicity due to caffeine is less likely, due to the relatively small amounts in this formulation.

Signs and Symptoms

Toxicity from ***barbiturate*** poisoning 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.

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 capsules)
Acetaminophen:	toxic dose	10 g	(b)(4) capsules)
Caffeine:	toxic dose	1 g	(25 capsules)

In all cases of suspected overdosage, call your Regional Poison Control Center to obtain the most up-to-date information about the treatment of overdosage. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®*.

DOSAGE AND ADMINISTRATION

One or 2 capsules every 4 hours as needed. Total daily dosage should not exceed 6 capsules.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED

Butalbital, Acetaminophen, and Caffeine capsules USP

Containing 50 mg butalbital, 325 mg acetaminophen, and 40 mg caffeine. Available as hard gelatin capsules with a yellow body and green cap, printed with NXG 7029, and supplied in bottles of 100 and 500.

Store [redacted] (b) (4) dispense in a tight container.

*Trademark of Medical Economics Company, Inc.

Rx only

Nexgen Pharma Inc.
Irvine, CA 92614-6502 USA

[redacted] (b) (4) **(Butalbital, Acetaminophen, and Caffeine Capsules, USP)**

PRODUCT INFO

Product Code	0722-7029	**Dosage Form**	CAPSULE
Route Of Administration	ORAL	**DEA Schedule**	

INGREDIENTS

Name (Active Moiety)	Type	Strength
butalbital, USP (butalbital, USP)	Active	50 MILLIGRAM In 1 CAPSULE
acetaminophen, USP (acetaminophen, USP)	Active	300 MILLIGRAM In 1 CAPSULE
caffeine, USP (caffeine, USP)	Active	40 MILLIGRAM In 1 CAPSULE
microcrystalline cellulose	Inactive	[redacted] (b) (4)
sodium lauryl sulfate	Inactive	
stearic acid	Inactive	
talc	Inactive	

IMPRINT INFORMATION

Characteristic	Appearance	Characteristic	Appearance
Color	GREEN (Green Cap) , YELLOW (Yellow Body)	**Score**	1
Shape	CAPSULE (Hard Gelatin Capsule)	**Symbol**	true
Imprint Code	NXG 7029	**Coating**	false
Size	13mm		

PACKAGING

#	NDC	Package Description	Multilevel Packaging
1	0722-7029-05	500 CAPSULE In 1 BOTTLE	None
2	0722-7029-01	100 CAPSULE In 1 BOTTLE	None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chan Park
7/19/2007 02:28:33 PM
Chan Park for Lillie Golson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040885

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 40885 Applicant Nexgen Pharma, Inc.
Drug Butalbital, Acetaminophen and Caffeine Capsules USP Strength(s) 50 mg/300 mg/40 mg

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 23 Sept 2009 Date _____
Chief, Reg. Support Branch Initials MHS Initials _____
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = _____ NDA# _____
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked _____
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 4/23/2007, BOS=Approved SP 2004P-0561, no relevant patents cert provided. SP 2004P-0561 was approved on 3/31/2005 and specifically permitted the applicant to submit an ANDA for Acetaminophen, Butalbital and Caffeine Capsules, 300 mg, 50 mg and 40 mg-the petition was based upon ANDA 89-007 which is approved for the same components in 325 mg/50 mg/ and 40 mg. ANDA ack for filing on 4/23/2007(LO dated 7/13/2007). There are no remaining unexpired patents or exclusivities which protect the RLD. This ANDA is eligible for immediate Full Approval.

2. Project Manager, Simon Eng Team 8 Review Support Branch Date 9/10/09 Date _____
Initials se Initials _____

Original Rec'd date 4/20/07
Date Acceptable for Filing 4/23/07
Patent Certification (type) PI
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/2/08
Date of Office Bio Review 2/28/08
Date of Labeling Approv. Sum 10/16/08
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date_____ Date 11/16/09
Name/Initials_____ Name/Initials rlw/for
Comments:

Hi Simon,

Please endorse the letter for me as well.

Thanks

From: Park, Chan H
Sent: Thursday, September 24, 2009 10:23 AM
To: Eng, Simon
Cc: Golson, Lillie D
Subject: FW: 40-885/Nexgen/Butalbital, Acetaminophen, and Caffeine Capsules USP Labeling Endorsement
Hi Simon,

Please endure the AP letter for me. Thanks,

Chan

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 11/16/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date11/10/09
Chemistry Div. II InitialsRCA

Comments:CMC OK, see attached spreadsheet.

6. Frank Holcombe **First Generics Only** Date 11/16/09
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved with this combination of active ingredients.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____

RLD = Butalbital, Acetaminophen and Caffeine Capsules, 50 mg/325 mg/40 mg
Mikart Inc. ANDA 89-007

8. Peter Rickman Date 11/16/09
Director, DLPS Initials rlw/for

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐ Comments: Bioequivalence waiver granted under 21 CFR 320.22(c). Nexgen will use USP dissolution specifications. Drug product was subject to DESI. Office-level bio endorsed 2/28/08.

Final-printed labeling (FPL) found acceptable for approval 10/16/08, as endorsed 9/24/09, above.

CMC found acceptable for approval (Chemistry Review #3).

OR

8. Robert L. West Date 11/16/09
Deputy Director, OGD Initials rlw/for
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 9/24/09 (Verified 11/16/09). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA was accepted for filing based upon an approved ANDA Suitability Petition (2004P-0561/CP1). The amount of acetaminophen differs from that provided by the RLD (ANDA = 300 mg) (RLD = 325 mg). This Suitability Petition was approved on March 31, 2005. This is acceptable.

9. Gary Buehler Date 11/16/09
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

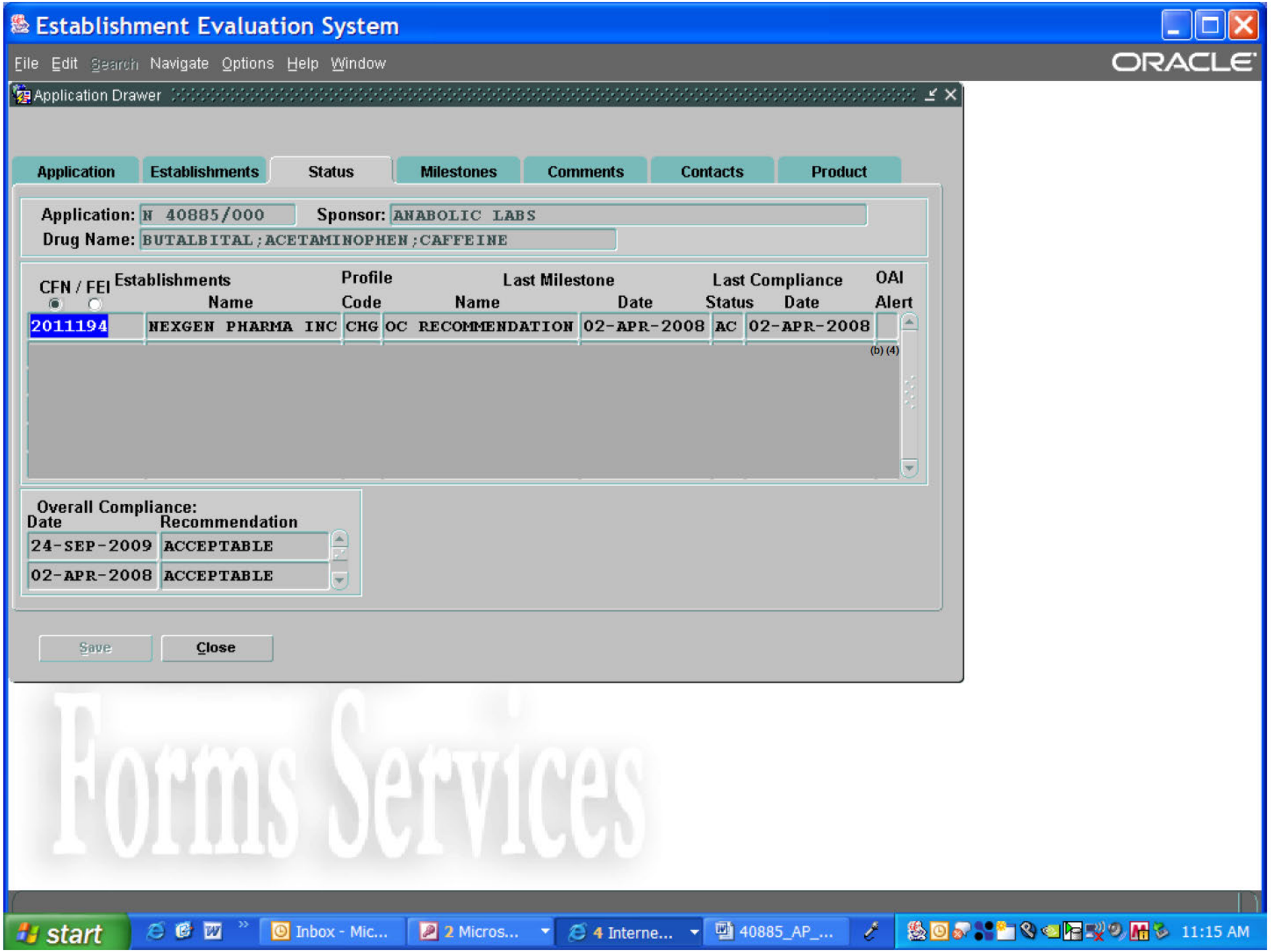
10. Project Manager, Simon Eng Team 8 Date11/16/2009

Review Support Branch Initials SE
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
1500Time notified of approval by phone
1500Time approval letter faxed

FDA Notification:
11/16/2009Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
11/16/2009Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA: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Application Drawer
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Status
Milestones
Comments
Contacts
Product
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Sponsor: ANABOLIC LABS
Drug Name: BUTALBITAL;ACETAMINOPHEN;CAFFEINE
CFN / FEI
Establishments Name
Profile Code
Last Milestone Name
Last Milestone Date
Last Compliance Status
Last Compliance Date
OAI Alert
2011194
NEXGEN PHARMA INC
CHG
OC RECOMMENDATION
02-APR-2008
AC
02-APR-2008
(b) (4)
Overall Compliance:
Date
Recommendation
24-SEP-2009
ACCEPTABLE
02-APR-2008
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start
Inbox - Mic...
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4 Interne...
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11:15 AM

COMIS TABLE:

--SELECT-- Appl # Suppl # Doc # Search

My Inbox|Check in Communication|Create Tracking Record|Queue|Reports|Search|Manage Drug Name Dictionary|Admin Logged in as: ROBERT WEST (Log Off)

DARRTS Home > Application Search > Application Search Results > View Application >

Application Type/Number: ANDA-040885 **Product Name:** BUTALBITAL;ACETAMINOPHEN;CAFFEINE **Dosage Form:** CAPSULE **Applicant:** ANABOLIC LABORATORIES INC **Responsible Organization:** CDER/OGD

Application History

Show only 20 rows | Export Results | Include NAI Previous 1-28 of 28 Next

	Supp. Document Number/Communication Author	Received/Communication Date	Sent Via	Submit/Final Date	Supporting Document Category/Subcategory / Communication Function	Copy
View	TANG, LUCIA C	09/23/2009	N/A	09/23/2009	REV-QUALITY-03(General Review)	Archive
View	12	09/18/2009		09/17/2009	Quality/Response To Information Request	
View	11	09/14/2009		09/11/2009	Quality/Quality Information	
View	10	03/10/2009		03/09/2009	Resubmission/After Action- Complete Quality/Quality Information	
View	PATEL, NITIN K	12/23/2008	MAIL	12/23/2008	COR-ANDAACTION-09(Complete Response)	Archive
View	TANG, LUCIA C	12/23/2008	N/A	12/23/2008	REV-QUALITY-03(General Review)	Archive
View	PARK, CHAN H	10/16/2008	N/A	10/16/2008	REV-RPM-04(Labeling Review)	Archive
View	9	06/04/2008		06/03/2008	Labeling/Other	View EDR
View	8	05/27/2008		05/23/2008	Resubmission/After Action- Complete	View

					Quality/Quality Information	EDR
View	PARK, CHAN H	04/11/2008	N/A	04/11/2008	REV-RPM-04(Labeling Review)	Archive
View	PARK, CHAN H	04/11/2008	MAIL	04/11/2008	COR-ANDADE-03(Labeling Deficiencies)	Archive
View	PATEL, NITIN K	03/06/2008	MAIL	03/06/2008	COR-ANDAACTION-05(Not Approvable-Minor Deficiencies)	Archive
View	TANG, LUCIA C	03/05/2008	N/A	03/05/2008	REV-QUALITY-03(General Review)	Archive
View	NWAKAMA, PATRICK E	02/28/2008	N/A	02/28/2008	REV-BIOEQ-02(Dissolution Review)	Archive
View	7	02/25/2008		02/20/2008	Correspondence	
View	6	02/21/2008		02/20/2008	Labeling/Other	View EDR
View	5	02/11/2008		02/07/2008	Correspondence	
View	4	12/06/2007		12/04/2007	Bioequivalence/Other	View EDR
View	MAZZELLA, STEVEN D	11/21/2007	MAIL	11/21/2007	COR-ANDADE-01(Bio Incomplete Deficiencies)	Archive
View	NWAKAMA, PATRICK E	11/19/2007	N/A	11/19/2007	REV-BIOEQ-01(General Review)	Archive
View	PARK, CHAN H	08/06/2007	MAIL	08/06/2007	COR-ANDADE-03(Labeling Deficiencies)	Archive
View	PARK, CHAN H	08/06/2007	N/A	08/06/2007	REV-RPM-04(Labeling Review)	Archive
View	PARK, CHAN H	07/19/2007	N/A	07/19/2007	FRM-CONSULT-07(Request for Proprietary Name Review)	Archive
View	3	07/19/2007		07/17/2007	Correspondence	
View	SHEPPERSON, STANLEY M	07/13/2007	N/A	07/13/2007	REV-RPM-03(Filing Review)	Archive
View	SHEPPERSON, STANLEY M	07/13/2007	MAIL	07/13/2007	COR-ANDAFILE-01(Filing Acknowledgment (General))	Archive
View	2	07/11/2007		07/10/2007	Correspondence	
View	1	04/23/2007		04/20/2007	New/ANDA	View EDR

Show only 20 rows | Export Results | Include NAI

Previous 1-28 of 28 Next

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 089007 Product 001 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2009
Patent and Generic Drug Product Data Last Updated: November 13, 2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-40885	ORIG-1	ANABOLIC LABORATORIES INC	BUTALBITAL;ACETAMINOPHEN ;CAFFEINE

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/s/

SIMON S ENG
11/16/2009

COMPLETE RESPONSE -- MINOR

ANDA 40-885

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Nexgen Pharma, Inc. TEL: 949-260-3704

ATTN: Robert van Osdel FAX: 949-261-2787

FROM: Nitin Patel FDA CONTACT PHONE: (240) 276-8548

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated April 20, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/300 mg/40 mg.

Reference is also made to your amendment dated May 23, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__**1**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Chemistry comments to be provided to the Applicant

ANDA: 40-885 APPLICANT: Nexgen Pharma, Inc.

DRUG PRODUCT: Butalbital, Acetaminophen, and Caffeine Capsules, USP 50 mg/300 mg/40 mg

The deficiencies presented below represent MINOR deficiencies:

1. (b) (4)
2.
3.
4.
5.

Sincerely yours,

{see appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Ubrani Venkataram
12/23/2008 02:57:19 PM
For Florence Fang

Telephone Fax

ANDA 40-885
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park
North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8974

TO: Nexgen Pharma, Inc.. TEL: 949-260-3704

ATTN: Robert Van Osdel FAX: 949-261-2787

FROM: Chan Park

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butalbital, Acetaminophen, and Caffeine Capsules.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments:

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

ANDA Number: 40-885 Date of Submission: February 20, 2008

Applicant's Name: Nexgen Pharma, Inc.

Established Name: Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg

Proposed Proprietary Name (b) (4)

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. We note that contrary to your statement, you still have the ANDA 89-660 as the RLD in your application. As addressed in the last deficiency letter, the "Esgic® Capsules (ANDA 89-660)" has been discontinued and the new RLD is the ANDA 89-007 (Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg). Please note that the new RLD does not have a proprietary name. Please revise your application form accordingly.

   b. Your proposed proprietary name, (b) (4) is still under review by the Office of Surveillance and Epidemiology. We will inform you of the comments when available.

2. CONTAINER - 100s and 500s

   a. See GENERAL COMMENT (a) above.

   b. (b) (4)

   c. Please ensure that all text appears sufficiently legible, particularly the "Usual Adult Dosage" section.

   d. Please note that for computer generated labeling to be acceptable as final print, it must be of actual size, color, and clarity. Please ensure that these criteria are met prior to submission of final print.

3. INSERT

   a. See GENERAL COMMENT (a) above.

   b. Please be advised that the requirements of 21 CFR 201.10(g) must be met. The established name must appear in certain sections in association with the proprietary name if the proprietary name is approved and used in the text.

We will not request the submission of the final printed labeling pending the review of your proposed proprietary name.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Lillie Golson
4/11/2008 11:42:07 AM
Lillie Golson for Wm. Peter Rickman

MINOR AMENDMENT

ANDA 40-885

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Nexgen Pharma, Inc. TEL: 949-260-3704

ATTN: Robert van Osdel FAX: 949-261-2787

FROM: Nitin Patel PROJECT MANAGER: (240) 276-8572

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated April 20, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/300 mg/40 mg.

Reference is also made to your amendment dated July 10, 2007.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (**2** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

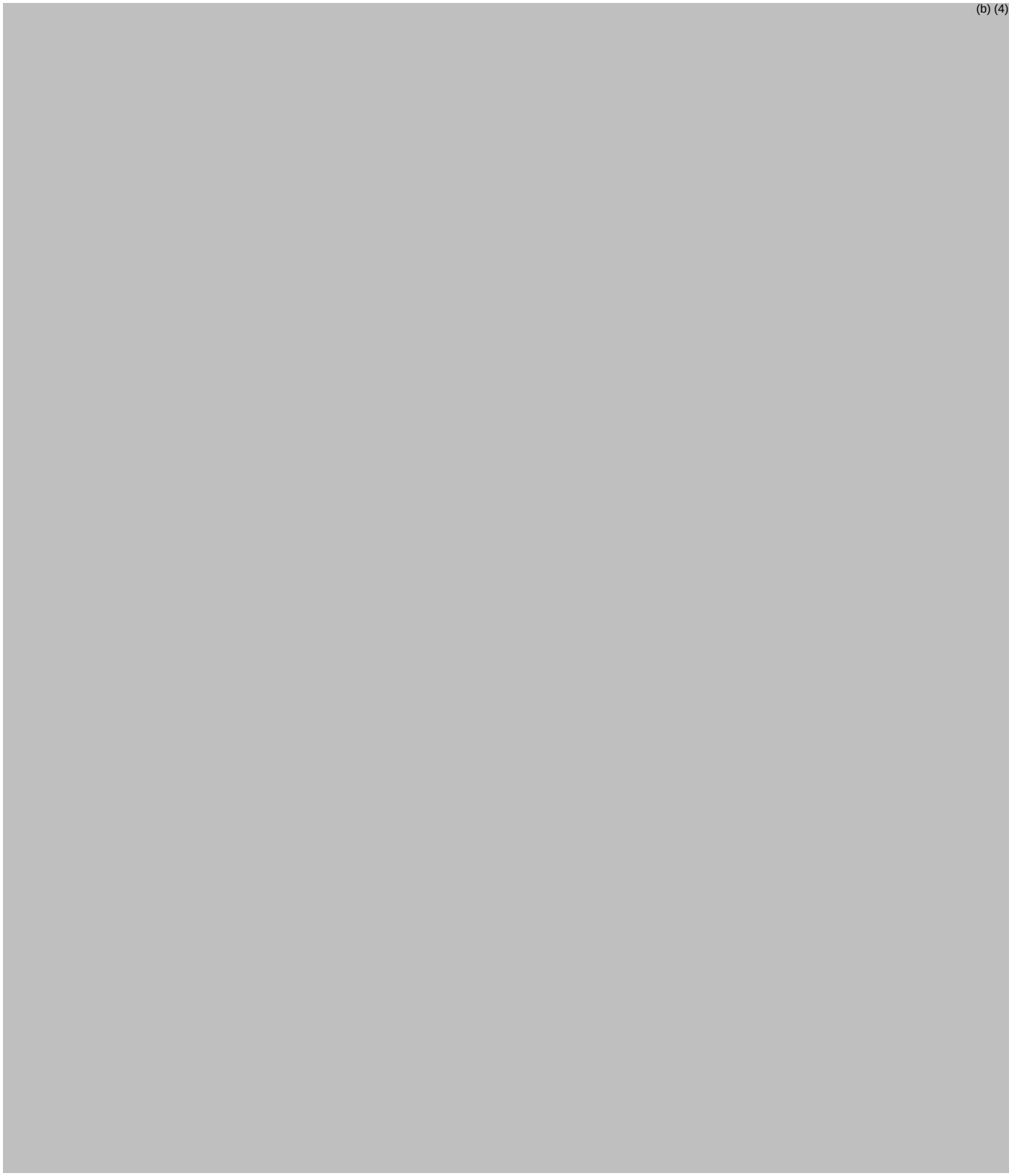
Chemistry comments to be provided to the Applicant

ANDA: 40-885 APPLICANT: Nexgen Pharma, Inc.

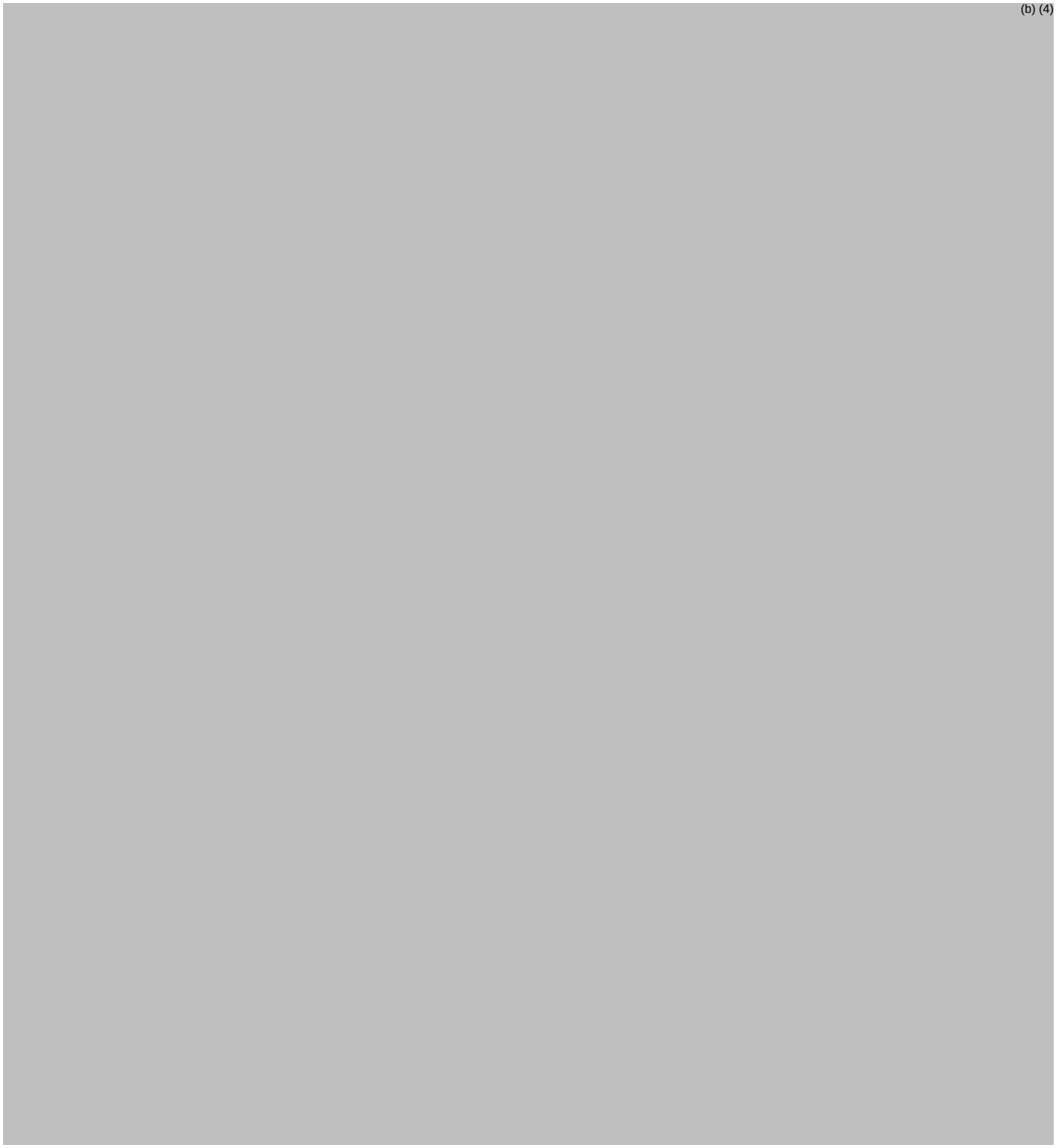
DRUG PRODUCT: Butalbital, Acetaminophen, and Caffeine Capsules, USP 50 mg/300 mg/40 mg

The deficiencies presented below represent MINOR deficiencies:

A. (b) (4)



(b) (4)



Sincerely yours,

{see appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Ubrani Venkataram
3/6/2008 11:15:43 AM
For Florence Fang

BIOEQUIVALENCY AMENDMENT

ANDA 40-885

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Anabolic Laboratories, Inc. TEL: 949-260-3704

ATTN: Robert van Osdel FAX: 949-261-2787

FROM: Steven Mazzella PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on April 20, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butalbital, Acetaminophen and Caffeine Capsules USP, 50 mg/300 mg/40 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

ANDA: 40885

APPLICANT: Anabolic Laboratories, Inc.

DRUG PRODUCT: Butalbital, Acetaminophen & Caffeine Capsules USP, 50 mg/300 mg/40 mg

The Division of Bioequivalence has completed its review and has no further questions at this time. The following deficiency has been identified:

Your proposed dissolution method (900 mL, Water, [redacted] (b) (4)) is not acceptable. Please repeat your dissolution testing using the current USP method:

Apparatus:	I (Basket)
Speed of Rotation:	100 rpm
Medium:	Water
Volume:	900 mL; 37°C
Specifications	NLT 80% *(Q)* in 60 minutes for all 3 components

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Dale Conner

11/21/2007 10:32:41 AM

Telephone Fax

ANDA 40-885
OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park
North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5864

TO: Nexgen Pharma, Inc. TEL: 949-260-3704

ATTN: Robert van Osdel FAX: 949-261-2787

FROM: Chan Park

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Butalbital, APAP , and Caffeine Capsules.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments:

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

ANDA Number: 40-885 Date of Submission: April 20, 2007

Applicant's Name: Nexgen Pharma, Inc.

Established Name: Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/300 mg/40 mg

Proposed Proprietary Name: (b) (4)

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. In your application form, you entered "Esgic® Capsules (89-007)" as the Reference Listed Drug for the basis for submission of this application. Please note that the ANDA for Esgic® capsules is 89-660, not 89-007. It appears that Esgic capsules (89-660) have been discontinued per the Electronic Orange Book. The ANDA 89-007 was assigned as a new RLD for Butalbital, Acetaminophen, and Caffeine Capsules USP, 50 mg/325 mg/40 mg. Please revise the application form accordingly.

   b. Your proposed proprietary name, (b) (4) was forwarded to the Office of Surveillance and Epidemiology for their review and comments. We will inform you of the comments when available.

   c. We note that you submitted your proposed insert labeling in SPL only. Please be advised that you still need to include the pdf. version in final printed format for approval. In addition, please include the MS Word version for ease of review.

   d. It appears that your SPL submitted failed validation. Please contact the SPL group at SPL@fda.hhs.gov for detail.

2. CONTAINER - 100s and 500s

   a. Revise to read as follows:

      Store and Dispense: Store at 20 to 25°C (68 to 77°C) [see USP Controlled Room Temperature] Dispense in a tight, light-resistant container.

   b. Please ensure that you complete the bar code prior to the submission of final printed labels.

3. INSERT

   a. DESCRIPTION

      i. Revise the molecular weight of butalbital to read "212.25 per the USP 30.

      ii. Revise the molecular weight of acetaminophen to read "151.16" per the USP 30.

   b. OVERDOSAGE - Toxic Doses (for adults), Acetaminophen:

      As your proposed formulation contains 300 mg of acetaminophen, not (b) (4), it should read "(33 capsules)" rather than (b) (4) Please revise and/or comment.

c. HOW SUPPLIED

i. First paragraph - Revise to read as follows:

Butalbital, Acetaminophen, and Caffeine Capsules USP,
50 mg/300 mg/40 mg

ii. Second paragraph - Revise to read:

Containing 50 mg butalbital, 300 mg acetaminophen, and 40 mg caffeine… [rather than (b) (4)

iii. We encourage the inclusion of NDC numbers.

d. DATA ELEMENT TABLE

i. Product name - Revise to read as follows, if your proposed name is found acceptable:

(b) (4)

ii. Ingredients

(b) (4)

iii. Appearance - Symbol:

We believe that your finished drug product does not contain the "symbol", but contains the imprint code only. Please revise to read (b) (4) rather than (b) (4)

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Jacqueline Council
8/6/2007 02:59:53 PM
for Wm. Peter Richman