

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 90-223

Name: Benztropine Mesylate Injection USP,
1 mg/mL, 2 mL vials

Sponsor: Nexus Pharmaceuticals Inc.

Approval Date: July 28, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-223

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-223

APPROVAL LETTER



ANDA 90-233

Nexus Pharmaceuticals Inc.
Attention: Shahid Ahmed
430 N. Milwaukee Avenue
Suite 9
Lincolnshire, IL 60069

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 14, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Benztropine Mesylate Injection USP, 1 mg/mL, 2 mL vials.

Reference is also made to your amendments dated October 6, 2008; February 12 and 18, May 6, and June 4, 2009.

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 your Benztropine Mesylate Injection USP, 1 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Cogentin Injection, 1 mg/mL, of Lundbeck Inc.

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.

We 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 505-1(i).

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(s) 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 90-233**".

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

THERESA C LIU
07/28/2009

ROBERT L WEST on behalf of GARY J BUEHLER
07/28/2009
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-223

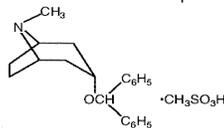
LABELING

Benztropine Mesylate Injection, USP

Rx Only

DESCRIPTION

Benztropine mesylate is a synthetic compound containing structural features found in atropine and diphenhydramine. It is designated chemically as 8-azabicyclo[3.2.1] octane, 3-(diphenylmethoxy)-, *endo*, methanesulfonate. Its empirical formula is $C_{21}H_{25}NO \cdot CH_3SO_3H$, and its structural formula is:



Benzotropine mesylate is a crystalline white powder, very soluble in water, and has a molecular weight of 403.54.

Benzotropine mesylate Injection is supplied as a sterile injection for intravenous and intramuscular use.

Each milliliter of the injection contains:

Benzotropine mesylate 1 mg/mL

Sodium chloride 9 mg/mL

Water for injection q.s. 1 mL

CLINICAL PHARMACOLOGY

Benzotropine mesylate possesses both anticholinergic and antihistaminic effects, although only the former have been established as therapeutically significant in the management of parkinsonism. In the isolated guinea pig ileum, the anticholinergic activity of this drug is about equal to that of atropine; however, when administered orally to unanesthetized cats, it is only about half as active as atropine.

In laboratory animals, its antihistaminic activity and duration of action approach those of pyrilamine maleate.

INDICATIONS AND USAGE

For use as an adjunct in the therapy of all forms of parkinsonism.

Useful also in the control of extrapyramidal disorders (except tardive dyskinesia --- see **PRECAUTIONS**) due to neuroleptic drugs (e.g., phenothiazines).

CONTRAINDICATIONS

Hypersensitivity to any component of benztropine mesylate injection.

Because of its atropine-like side effects, this drug is contraindicated in pediatric patients under three years of age, and should be used with caution in older pediatric patients.

WARNINGS

Safe use in pregnancy has not been established.

Benzotropine mesylate may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

When benztropine mesylate is given concomitantly with phenothiazines, haloperidol, or other drugs with anticholinergic or anti-dopaminergic activity, patients should be advised to report gastrointestinal complaints, fever or heat intolerance promptly. Paralytic ileus, hyperthermia and heat stroke, all of which have sometimes been fatal, have occurred in patients taking anti-cholinergic-type antiparkinsonism drugs, including benztropine mesylate, in combination with phenothiazines and/or tricyclic antidepressants.

Since benztropine mesylate contains structural features of atropine, it may produce anhidrosis. For this reason, it should be administered with caution during hot weather, especially when given concomitantly with other atropine-like drugs to the chronically ill, the alcoholic, those who have central nervous system disease, and those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, the possibility of hyperthermia should be considered. Dosage should be decreased at the discretion of the physician so that the ability to maintain body heat equilibrium by perspiration is not impaired. Severe anhidrosis and fatal hyperthermia have occurred.

PRECAUTIONS

General

Since benztropine mesylate has cumulative action, continued supervision is advisable. Patients with a tendency to tachycardia and patients with prostatic hypertrophy should be observed closely during treatment.

Dysuria may occur, but rarely becomes a problem. Urinary retention has been reported with benztropine mesylate.

The drug may cause complaints of weakness and inability to move particular muscle groups, especially in large doses. For example, if the neck has been rigid and suddenly relaxes, it may feel weak, causing some concern. In this event, dosage adjustment is required.

Mental confusion and excitement may occur with large doses, or in susceptible patients. Visual hallucinations have been reported occasionally. Furthermore, in the treatment of extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines), in patients with mental disorders, occasionally there may be intensification of mental symptoms. In such cases, antiparkinsonian drugs can precipitate a toxic psychosis. Patients with mental disorders should be kept under careful observation, especially at the beginning of treatment or if dosage is increased. Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia, and in some instances may aggravate them. Benztropine mesylate is not recommended for use in patients with tardive dyskinesia.

The physician should be aware of the possible occurrence of glaucoma. Although the drug does not appear to have any adverse effect on simple glaucoma, it probably should not be used in angle-closure glaucoma.

Drug Interactions

Antipsychotic drugs such as phenothiazines or haloperidol; tricyclic antidepressants (see **WARNINGS**).

Pediatric use

Because of the atropine-like side effects, benztropine mesylate should be used with caution in pediatric patients over three years of age (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

The adverse reactions below, most of which are anticholinergic in nature, have been reported and within each category are listed in order of decreasing severity.

Cardiovascular Tachycardia.

Digestive Paralytic ileus, constipation, vomiting, nausea, dry mouth.

If dry mouth is so severe that there is difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue the drug temporarily. Slight reduction in dosage may control nausea and still give sufficient relief of symptoms. Vomiting may be controlled by temporary discontinuation, followed by resumption at a lower dosage.

Nervous System Toxic psychosis, including confusion, disorientation, memory impairment, visual hallucinations; exacerbation of pre-existing psychotic symptoms; nervousness; depression; listlessness; numbness of fingers.

Special Senses Blurred vision, dilated pupils.

Urogenital Urinary retention, dysuria.

Metabolic/Immune or Skin Occasionally, an allergic reaction, e.g., skin rash, develops. If this cannot be controlled by dosage reduction, the medication should be discontinued.

Other Heat stroke, hyperthermia, fever.

OVERDOSAGE

Manifestations May be any of those seen in atropine poisoning or antihistamine overdose: CNS depression, preceded or followed by stimulation; confusion; nervousness; listlessness; intensification of mental symptoms or toxic psychosis in patients with mental illness being treated with neuroleptic drugs (e.g., phenothiazines); hallucinations (especially visual); dizziness; muscle weakness; ataxia; dry mouth; mydriasis; blurred vision; palpitations; tachycardia; elevated blood pressure; nausea; vomiting; dysuria; numbness of fingers; dysphagia; allergic reactions, e.g., skin rash; headache; hot, dry, flushed skin; delirium; coma; shock; convulsions; respiratory arrest; anhidrosis; hyperthermia; glaucoma; constipation.

Treatment Physostigmine salicylate, 1 to 2 mg, SC or IV, reportedly will reverse symptoms of anticholinergic intoxication¹. A second injection may be given after 2 hours if required. Otherwise treatment is symptomatic and supportive. Induce emesis or perform gastric lavage (contraindicated in precomatose, convulsive, or psychotic states). Maintain respiration. A short-acting barbiturate may be used for CNS excitement, but with caution to avoid subsequent depression; supportive care for depression (avoid convulsant stimulants such as picrotoxin, pentyleneetetrazol, or bemegride); artificial respiration for severe respiratory depression; a local miotic for mydriasis and cycloplegia; ice bags or other cold applications and alcohol sponges for hyperpyrexia, a vasopressor and fluids for circulatory collapse. Darken room for photophobia.

DOSAGE AND ADMINISTRATION

Since there is no significant difference in onset of effect after intravenous or intramuscular injection, usually there is no need to use the intravenous route. The drug is quickly effective after either route, with improvement sometimes noticeable a few minutes after injection. In emergency situations, when the condition of the patient is alarming, 1 to 2 mL of the injection normally will provide quick relief. If the parkinsonian effect begins to return, the dose can be repeated.

Because of cumulative action, therapy should be initiated with a low dose which is increased gradually at five or six-day intervals to the smallest amount necessary for optimal relief. Increases should be made in increments of 0.5 mg, to a maximum of 6 mg, or until optimal results are obtained without excessive adverse reactions.

Postencephalitic and Idiopathic Parkinsonism

The usual daily dose is 1 to 2 mg, with a range of 0.5 to 6 mg parenterally.

As with any agent used in parkinsonism, dosage must be individualized according to age and weight, and the type of parkinsonism being treated. Generally, older patients, and thin patients cannot tolerate large doses. Most patients with postencephalitic parkinsonism need fairly large doses and tolerate them well. Patients with a poor mental outlook are usually poor candidates for therapy.

In idiopathic parkinsonism, therapy may be initiated with a single daily dose of 0.5 to 1 mg at bedtime. In some patients, this will be adequate; in others 4 to 6 mg a day may be required.

In postencephalitic parkinsonism, therapy may be initiated in most patients with 2 mg a day in one or more doses. In highly sensitive patients, therapy may be initiated with 0.5 mg at bedtime, and increased as necessary.

Some patients experience greatest relief by taking the entire dose at bedtime; others react more favorably to divided doses, two to four times a day. Frequently, one dose a day is sufficient, and divided doses may be unnecessary or undesirable.

The long duration of action of this drug makes it particularly suitable for bedtime medication when its effects may last throughout the night, enabling patients to turn in bed during the night more easily, and to rise in the morning.

When benzotropine mesylate is started, do not terminate therapy with other antiparkinsonian agents abruptly. If the other agents are to be reduced or discontinued, it must be done gradually. Many patients obtain greatest relief with combination therapy.

Benzotropine mesylate may be used concomitantly with SINEMET* (Carbidopa-Levodopa), or with levodopa, in which case periodic dosage adjustment may be required in order to maintain optimum response.

Drug-Induced Extrapyramidal Disorders

In treating extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines), the recommended dosage is 1 to 4 mg once or twice a day parenterally. Dosage must be individualized according to the need of the patient. Some patients require more than recommended; others do not need as much.

In acute dystonic reaction, 1 to 2 mL of the injection usually relieves the condition quickly.

When extrapyramidal disorders develop soon after initiation of treatment with neuroleptic drugs (e.g., phenothiazines), they are likely to be transient. One to 2 mg of benzotropine mesylate two or three times a day usually provides relief within one or two days. After one or two weeks, the drug should be withdrawn to determine the continued need for it. If such disorders recur, benzotropine mesylate can be reinstated.

Certain drug-induced extrapyramidal disorders that develop slowly may not respond to benzotropine mesylate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Injection benzotropine mesylate, 1 mg per mL, is a clear, colorless solution and is supplied in boxes of 5 x 2 mL vials.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59 to 86°F) [see USP Controlled room temperature], protect from light, retain in carton until time of use.

NDC Number 14789-300-02

Manufactured in the USA for: Nexus Pharmaceuticals, Inc., Lincolnshire, IL 60069

May 2009

PM-30100

¹ Duvoisin, R.C.; Katz, R.J.; Amer. Med. Ass. 206:1963-1965, Nov.25, 1968

*Registered trademark of MERCK & CO., Inc.

(b) (4)

proof date	06/01/09	06/03/09	06/04/09			
version no.	1	2	3			

This Proof **MUST BE SIGNED & RETURNED** to

(b) (4)



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Deline



(b) (4) 3/4/09 3:18 PM
Deline

(b) (4)

LABEL SIZE: 0.75 X 1.625 .125 CR

PROOF IS AT 100%

COLORS

NOTE: PMS Swatch on proof does not represent exact color.

(b) (4)

proof approval

reproof required

date	authorized signature

(b) (4)

5 x 2 mL Single Dose Vials
NDC 14789-300-02
Manufactured in the USA for
NEXUS PHARMACEUTICALS, INC. Lincolnshire, IL 60069

BENZTROPINE MESYLATE
INJECTION, USP
2 mg/ 2 mL (1 mg/ mL)
Rx Only

BENZTROPINE MESYLATE
INJECTION, USP
2 mg/ 2 mL (1 mg/ mL)
Rx Only

Each mL Contains:
Active: Benztropine Mesylate: 1 mg
Inactives: Sodium Chloride 9 mg,
Water for Injection, q.s.

no
varnish

Usual Dosage:
For parkinsonism,
1 to 2 mg daily.

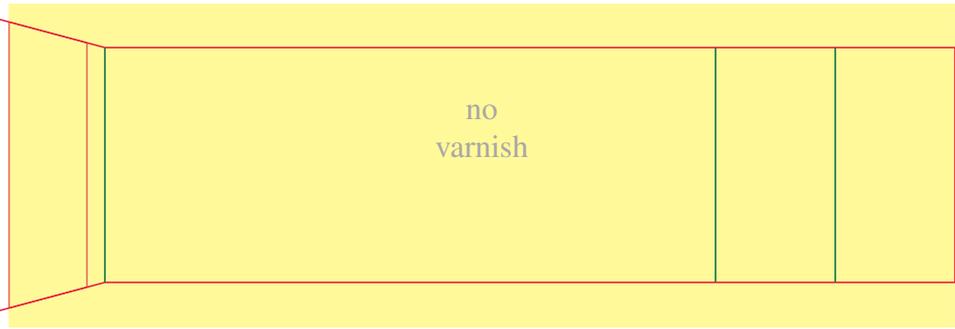
For drug induced
extrapyramidal
disorders, 1 to 4 mg
once or twice a day.
See accompanying
package insert.

BENZTROPINE MESYLATE
INJECTION, USP
2 mg/ 2 mL (1 mg/ mL)
Rx Only

Each mL Contains:
Active: Benztropine Mesylate: 1 mg
Inactives: Sodium Chloride 9 mg, Water for Injection, q.s.
5 x 2 mL Single Dose Vials
NDC 14789-300-02
FOR INTRAVENOUS OR INTRAMUSCULAR USE
Manufactured in the USA for
NEXUS PHARMACEUTICALS, INC. Lincolnshire, IL 60069

Storage:
Store at 25°C (77°F):
excursions permitted
to 15° to 30°C (59
to 86°F) [see USP
Controlled Room
Temperature]
Protect from light.
Retain in carton until
time of use.

PC-40240



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90-223

LABELING REVIEWS

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

ANDA Number: 90-233

Date of Submission: December 14, 2007 (Original)

Applicant's Name: Nexus Pharmaceuticals, Inc.

Established Name: Benzotropine Mesylate Injection USP, 2 mg/2 mL (1 mg/mL), 2 mL Single Dose Vials

Labeling Deficiencies:

1. CONTAINER (2 mL Single Dose Vial)
 - a. Please revise the expression of strength to read "2 mg/2 mL (1 mg/mL)" and delete "(b) (4)".
 - b. Please replace "(b) (4)" with "2 mL Single Dose Vial".
2. CARTON (5 x 2 mL Single Dose Vials)
 - a. Please revise the expression of strength to read "2 mg/2 mL (1 mg/mL)".
 - b. Please replace "(b) (4)" with "5 x 2 mL Single Dose Vials".
 - c. Please relocate "Rx Only" to the principal display panel.
 - d. Please relocate "FOR INTRAVENOUS OR INTRAMUSCULAR USE" to the principal display panel.
 - e. Please add the following statement after the "Protect from light" statement: "Retain in carton until time of use."
3. INSERT
 - a. GENERAL COMMENT – Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.
 - b. DOSAGE AND ADMINISTRATION, Postencephalitic and Idiopathic Parkinsonism
 - i. Fifth paragraph, first sentence – "...relief by taking..."
 - ii. Eighth paragraph – Please add an asterisk after "SINEMET" and add the following endnote: "*Registered trademark of MERCK & CO., Inc."
 - c. HOW SUPPLIED – Please add the storage temperature statement.

Please revise your labels and labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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 submission with all differences annotated and explained.

{See appended electronic signature page}

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

NOTES AND QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

(Part of this section came from Chemistry Review #2)

1. MODEL LABELING:
Cogentin Injection, NDA 12-015/S-023 approved May 21, 2001.
2. PATENTS/EXCLUSIVITIES:
There are no unexpired patents or exclusivities for this product
3. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

RLD	ANDA
Benztropine Mesylate, USP 1 mg	Benztropine Mesylate, USP 1 mg
Sodium Chloride, USP 9 mg	Sodium Chloride, USP 9 mg
Water For Injection q.s. 1 mL	Water For Injection q.s. 1 mL

4. STORAGE AND DISPENSING STATEMENT:
 - USP: Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
 - RLD: None
 - ANDA: Carton: "Store at 25°C (77°F); excursions permitted to 15° to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from light." Vial: None. Insert: None
 - **Firm is asked to add a storage temperature statement to the insert.**
 - Accelerated 40±2°C & 75% ±5% RH; Controlled room temperature 25±2°C & 60% ±5% RH
5. PACKAGE CONFIGURATION:
 - RLD: boxes of 5 x 2 mL ampuls per the current labeling
 - ANDA: boxes of 5 x 2 mL vials
6. CONTAINER/CLOSURE:
 - Vial: 2 cc Flint Type I Glass Vial
 - Stopper: 13 mm (b) (4) Rubber Stopper (synthetic rubber)
 - Seal: 13 mm Aluminum Flip-off White Seal
 - Per Chemistry Review #2: "...the glass vials were also tested using USP <661> to assure that it meets the current compendial physico-chemical testing criteria."
7. FINISHED DOSAGE FORM:
 - RLD: clear, colorless solution
 - ANDA: clear, colorless solution
8. MANUFACTURER
(b) (4)

Manufactured for Nexus Pharmaceuticals, Inc., Lincolnshire, IL

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

Review – NA1

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/s/

Soojung Sarah Park
3/30/2009 06:09:39 PM
LABELING REVIEWER

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

ANDA Number: 90-233

Date of Submission: May 6, 2009 (Amendment)

Applicant's Name: Nexus Pharmaceuticals, Inc.

Established Name: Benzotropine Mesylate Injection USP, 2 mg/2 mL (1 mg/mL), 2 mL Single Dose Vials

Labeling Deficiencies:

1. CONTAINER (2 mL Single Dose Vial)
 - a. Please increase the prominence of the established name and strength.
 - b. Please revise the expression of strength to read "2 mg/2 mL (1 mg/mL)". [insert spaces]
 - c. Please ensure that the primary expression of strength ("2 mg/2 mL") appears more prominently than the secondary strength ["(1 mg/mL)"].
2. CARTON (5 x 2 mL Single Dose Vials)
 - a. Please add "5 x 2 mL Single Dose Vials" to the principal display panel (the panel which contains the statement "FOR INTRAVENOUS OR INTRAMUSCULAR USE").
 - b. Please ensure that the expression of quantity does not appear in conjunction with the expression of strength.
3. INSERT
 - a. Please make the following revisions in accordance with 21 CFR 201.56.
 - i. Please replace the section heading '(b) (4)' with "CLINICAL PHARMACOLOGY".
 - ii. Please replace the section heading "INDICATIONS" with "INDICATIONS AND USAGE".
 - iii. Please relocate the "OVERDOSAGE" section to appear before the "DOSAGE AND ADMINISTRATION" section.
 - b. HOW SUPPLIED – "86°C" rather than '(b) (4)'

Please revise your labels and labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

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 submission with all differences annotated and explained.

{See appended electronic signature page}

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

NOTES AND QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

(Part of this section came from Chemistry Review #2)

1. **MODEL LABELING:**
Cogentin Injection, NDA 12-015/S-023, approved May 21, 2001
2. **PATENTS/EXCLUSIVITIES:**
There are no unexpired patents or exclusivities for this product.
3. **INACTIVE INGREDIENTS:**
The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

RLD	ANDA
Benztropine Mesylate, USP 1 mg	Benztropine Mesylate, USP 1 mg
Sodium Chloride, USP 9 mg	Sodium Chloride, USP 9 mg
Water For Injection q.s. 1 mL	Water For Injection q.s. 1 mL

4. **STORAGE AND DISPENSING STATEMENT:**
 - USP 32: Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
 - RLD: None
 - ANDA: Insert and Carton: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from light. Retain in carton until time of use. Vial: None.
 - Accelerated 40±2°C & 75% ±5% RH; Controlled room temperature 25±2°C & 60% ±5% RH
5. **PACKAGE CONFIGURATION:**
 - RLD: boxes of 5 x 2 mL ampuls per the current labeling
 - ANDA: boxes of 5 x 2 mL vials
6. **CONTAINER/CLOSURE:**
 - Vial: 2 cc Flint Type I Glass Vial
 - Stopper: 13 mm (b) (4) Rubber Stopper (synthetic rubber)
 - Seal: 13 mm Aluminum Flip-off White Seal
 - Per Chemistry Review #2: "...the glass vials were also tested using USP <661> to assure that it meets the current compendial physico-chemical testing criteria."
7. **FINISHED DOSAGE FORM:**
 - RLD: clear, colorless solution
 - ANDA: clear, colorless solution
8. **MANUFACTURER**
Manufactured by (b) (4)
Manufactured for Nexus Pharmaceuticals, Inc., Lincolnshire, IL

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

Review – NA2

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this page is the manifestation of the electronic signature.**

/s/

Soojung Sarah Park
5/20/2009 03:44:46 PM
LABELING REVIEWER

**APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 90-233

Date of Submission: June 4, 2009 (Amendment)

Applicant's Name: Nexus Pharmaceuticals, Inc.

Established Name: Benztropine Mesylate Injection USP, 2 mg/2 mL (1 mg/mL), 2 mL Single Dose Vials

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

Do you have Final Printed Labels and Labeling? E-submission

	Date Submitted	Recommendation
CONTAINER (2 mL Single Dose Vial)	June 4, 2009	Acceptable for Approval
CARTON (5 x 2 mL Single Dose Vials)	June 4, 2009	Acceptable for Approval
INSERT	June 4, 2009	Acceptable for Approval

Revisions needed post-approval: Yes

1. CONTAINER (2 mL Single Dose Vial)
In the expression of strength, replace "...1 mg/1 mL" with "...1 mg/mL".
 2. CARTON (5 x 2 mL Single Dose Vials)
 - a. In the expression of strength, please delete the space following "/".
 - b. Please increase the prominence of the expression of quantity, "5 x 2 mL Single Dose Vials", appearing on the principle display panel (the panel which contains the statement "FOR INTRAVENOUS OR INTRAMUSCULAR USE").
-

NOTES AND QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

(Part of this section came from Chemistry Review #2)

1. MODEL LABELING:
Cogentin Injection, NDA 12-015/S-023, approved May 21, 2001
2. PATENTS/EXCLUSIVITIES:
There are no unexpired patents or exclusivities for this product.
3. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

RLD	ANDA
Benztropine Mesylate, USP 1 mg	Benztropine Mesylate, USP 1 mg
Sodium Chloride, USP 9 mg	Sodium Chloride, USP 9 mg
Water For Injection q.s. 1 mL	Water For Injection q.s. 1 mL

4. STORAGE AND DISPENSING STATEMENT:
 - USP 32: Packaging and storage— Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.
 - RLD: None
 - ANDA: Insert and Carton: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Protect from light. Retain in carton until time of use. Vial: None.
 - Accelerated 40±2°C & 75% ±5% RH; Controlled room temperature 25±2°C & 60% ±5% RH
5. PACKAGE CONFIGURATION:
 - RLD: boxes of 5 x 2 mL ampuls per the current labeling
 - ANDA: boxes of 5 x 2 mL vials
6. CONTAINER/CLOSURE:
 - Vial: 2 cc Flint Type I Glass Vial
 - Stopper: 13 mm (b) (4) Rubber Stopper (synthetic rubber)
 - Seal: 13 mm Aluminum Flip-off White Seal
 - Per Chemistry Review #2: "...the glass vials were also tested using USP <661> to assure that it meets the current compendial physico-chemical testing criteria."
7. FINISHED DOSAGE FORM:
 - RLD: clear, colorless solution
 - ANDA: clear, colorless solution
8. MANUFACTURER
Manufactured by (b) (4)
Manufactured for Nexus Pharmaceuticals, Inc., Lincolnshire, IL

Primary Reviewer: Sarah Park

Team Leader: Koung Lee

AP Summary

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

/s/

Soojung Sarah Park
7/1/2009 03:01:35 PM
LABELING REVIEWER

This ANDA is on the AP Matrix

Koung Lee
7/1/2009 05:17:22 PM
LABELING REVIEWER

Labeling Reviewer will ask firm to relocate the route
of administration, "For IV or IM", to appear
just after the strength and also to appear
on all the panels along with the established
name.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90-223

CHEMISTRY REVIEWS

ANDA 90-233

Benztropine Mesylate Injection, USP
1 mg/mL (2 mg/2 mL)

NEXUS Pharmaceuticals, Inc.

Sema Basaran, Ph.D.
Office of Generic Drugs/Division of Chemistry II

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III. List Of Deficiencies To Be Communicated.....	

Chemistry Review Data Sheet

1. ANDA: #90-233
2. REVIEW #: 1
3. REVIEW DATE: 8/8/08
4. REVIEWER: Sema Basaran, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NA	
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	December 14, 2007
7. NAME & ADDRESS OF APPLICANT:

Name: Nexus Pharmaceuticals Inc.
430 N. Milwaukee Ave., Suite 9 Lincolnshire,
IL 60069 - USA

US Representative : N/A
Representative: Shahid Ahmed, Co-president
Telephone: (847)-913-2720
Fax (847)-913-2721
8. DRUG PRODUCT NAME/CODE/TYPE:
 - a) Proprietary Name: NA
 - b) Non-Proprietary Name (USAN): Benzotropine Mesylate Injection
9. LEGAL BASIS FOR SUBMISSION:

The basis for Nexus's proposed Benzotropine Mesylate Injection 1 mg/1 mL is the approved application for Cogentin[®] NDA #12-015 held by Merck.
10. PHARMACOL. CATEGORY: It is an Antimuscarinic used as an adjunct therapy for Parkinsonian.

11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 1 mg/ 1 mL
13. ROUTE OF ADMINISTRATION: Intramuscular or Intravenous
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

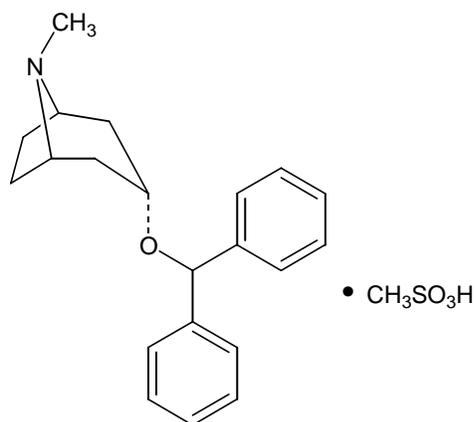
Chemical Nomenclature

The drug is known in literature as [3-(diphenylmethoxy)-8-methyl-8-azabicyclo[3,2,1] octane methanesulfonate.

Generic Nomenclature

Benztropine Mesylate

Molecular Structure



Molecular Formula

Benzotropine Mesylate: C₂₁H₂₅NO·CH₄O₃S

Molecular Weight

Benzotropine Mesylate: 403.54

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
N/A	II	(b) (4)		4			
(b) (4)	III			4			
	III			4			
N/A	III						

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 NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		
EA	Exclusion		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-233

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable – Minor deficiencies have been addressed in the review.

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

N/A

II. Summary of Chemistry Assessments

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

Benztropine Mesylate drug substance is a white to off white crystalline powder very soluble in water. The drug substance is subject of a USP monograph. The drug substance and the impurities are well characterized.

The drug product Bzotropine Mesylate Injection is (b) (4) product and is also the subject of a USP monograph.

The drug product is packaged in a 2 mL vials, clear glass, Type I (2 mg/2mL). Accelerated and stability testing support the firm's 24 month expiration dating period.

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

The maximum daily dosage is 6.0 mg/day administered intravenously or intramuscularly used for the symptomatic treatment of Parkinsons Disease.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is not recommended for approval until all issues have been adequately resolved.

Following this page, 42 pages withheld in full - (b)(4) Chemistry Review #1



CHEMISTRY REVIEW



Chemistry Assessment Section

3. Please provide updated stability data for the exhibit batch.

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



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 90-233
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-645/S.Basaran/ 8/15/08
HFD-645/DMaldonado/9/23/08
HFD-617/TLiu/9/24/08

V:\Firmsanz\Nexusus\Ltrs&Rev\90233N01.RSB.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/

Karen A. Bernard
9/24/2008 10:08:36 AM
CHEMIST
signing for Seam Basaran reviewer

Theresa Liu
9/24/2008 10:33:32 AM
CSO

Damaris Maldonado
9/26/2008 10:15:25 AM
CHEMIST

ANDA 90-233

**Benztropine Mesylate Injection, USP
1 mg/mL (2 mg/2 mL)**

NEXUS Pharmaceuticals, Inc.

**Sema Basaran, Ph.D.
Office of Generic Drugs/Division of Chemistry II**

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B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	7
Chemistry Assessment	8
III. List Of Deficiencies To Be Communicated.....	

Chemistry Review Data Sheet

1. ANDA: #90-233
2. REVIEW #: 2
3. REVIEW DATE: 11/22/08
4. REVIEWER: Sema Basaran, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	December 14, 2007
Acknowledgement Letter	July 8, 2008.
FDA Minor deficiency letter	September 26, 2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Minor Amendment	October 6, 2008

7. NAME & ADDRESS OF APPLICANT:

Name: Nexus Pharmaceuticals Inc.
430 N. Milwaukee Ave., Suite 9 Lincolnshire,
IL 60069 - USA

US Representative : N/A

Representative: Shahid Ahmed, Co-president

Telephone: (847)-913-2720

Fax (847)-913-2721

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: NA
- b) Non-Proprietary Name (USAN): Benzotropine Mesylate Injection

9. LEGAL BASIS FOR SUBMISSION:

The basis for Nexus's proposed Benzotropine Mesylate Injection 1 mg/1 mL is the approved application for Cogentin[®] NDA #12-015 held by Merck.

10. PHARMACOL. CATEGORY: It is an Antimuscarinic used as an adjunct therapy for Parkinsonian.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1 mg/ 1 mL

13. ROUTE OF ADMINISTRATION: Intramuscular or Intravenous

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

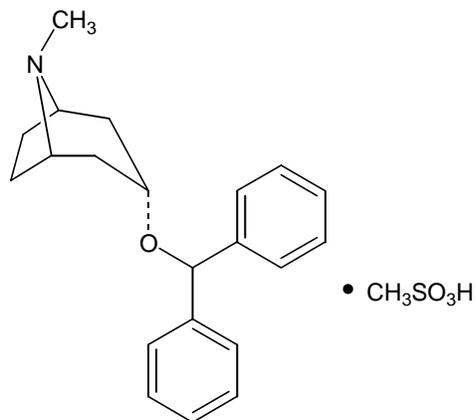
Chemical Nomenclature

The drug is known in literature as [3-(diphenylmethoxy)-8-methyl-8-azabicyclo[3,2,1] octane methanesulfonate.

Generic Nomenclature

Benztropine Mesylate

Molecular Structure



Molecular Formula

Benztropine Mesylate: C₂₁H₂₅NO.CH₄O₃S

Molecular Weight

Benztropine Mesylate: 403.54

17. RELATED/SUPPORTING DOCUMENTS:**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
N/A	II	(b) (4)	(b) (4)	4			
(b) (4)	III	(b) (4)	(b) (4)	4			
(b) (4)	III	(b) (4)	(b) (4)	4			
N/A	III	(b) (4)	(b) (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 NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	2/25/09	E. Adeeku
EES	Acceptable	6/18/09	
Methods Validation	N/A		
Labeling	Acceptable	7/1/09	S. Park
Bioequivalence	Acceptable	9-18-2008	Z.Zhao
EA	Exclusion		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below: Minor Amendment.

The Chemistry Review for ANDA 90-233

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable based on CMC status.

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

N/A

II. Summary of Chemistry Assessments

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

Benztropine Mesylate drug substance is a white to off white crystalline powder very soluble in water. The drug substance is subject of a USP monograph. The drug substance and the impurities are well characterized.

The drug product Bzotropine Mesylate Injection is (b) (4) product and is also the subject of a USP monograph.

The drug product is packaged in a 2 mL vials, clear glass, Type I (2 mg/2mL). Accelerated and stability testing support the firm's 24 month expiration dating period.

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

The maximum daily dosage is 6.0 mg/day administered intravenously or intramuscularly used for the symptomatic treatment of Parkinsons Disease.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is recommended for approval based on the acceptable CMC status.

Following this page, 46 pages withheld in full - (b)(4) Chemistry Review #2



CHEMISTRY REVIEW



Chemistry Assessment Section

(
Benzotropine Mesylate Injection, USP 1 mg/mL, Exhibit Batch Lot #082407, Batch Size (b) (4)
Container-Closure: 2cc Type I Glass Vial (b) (4) **Stopper, Flip-Off Aluminum Seal,**
API Manufacturer: (b) (4)
Date Manufactured: August 24, 2007, Stability Start Date August 30, 2007

Fill Size 2 mL

Test	Specification	(25 ± 2 °C / 60 ± 5% RH)								
		Initial	3 months		6 months		9 months		12 months	
			Upright	Inverted	Upright	Inverted	Upright	Inverted	Upright	Inverted
(b) (4)										

cc: ANDA 90-233
 DIV FILE
 Field Copy

Endorsements (Draft and Final with Dates):

HFD-645/S.Basaran/ 11/24/08
 HFD-645/DMaldonado/12/19/08
 HFD-617/TLiu/7/2/09

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TYPE OF LETTER: APPROVABLE

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

/s/

Theresa Liu
7/23/2009 12:49:46 PM
CSO
Check in for Sema Basaran

Damaris Maldonado
7/23/2009 12:50:29 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90-223

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90-233
Drug Product Name	Benztropine Mesylate Injection, USP
Strength(s)	1 mg/mL as 2 mL vials
Applicant Name	Nexus Pharmaceuticals Inc.
Address	430 N Milwaukee Ave., Suite 9 Lincolnshire, IL 60069
Applicant's Point of Contact	Shahid Ahmed Co-President
Contact's Telephone Number	847-913-2720
Contact's Fax Number	847-913-2721
Original Submission Date(s)	December 14, 2007
Submission Date(s) of Amendment(s) Under Review	None
Reviewer	Zhuojun Zhao, Ph.D.
OUTCOME DECISION	Acceptable

Review of a Waiver Request

1 EXECUTIVE SUMMARY

The firm has submitted a request for waiver of *in vivo* bioavailability / bioequivalence study requirements based on 21 CFR §320.22(b)(1) for its proposed product, Benztropine Mesylate Injection USP, 1mg / mL vials. The reference listed drug (RLD) is Ovation Pharmaceuticals' Cogentin® (Benztropine Mesylate Injection USP) 1mg / mL, approved in NDA 12-015.

The test product contains the same active and inactive ingredients as the RLD, and are quantitatively and qualitatively (Q1/Q2) identical. Therefore, the Division of Bioequivalence deems that the test product, Benztropine Mesylate Injection USP, 1mg/mL is bioequivalent to the reference product, Ovation Pharmaceuticals' Cogentin® 1mg/mL. The waiver of *in vivo* bioequivalence study requirements for the test product, Benztropine Mesylate Injection USP, 1mg/mL is **granted** as per 21 CFR §320.22 (b)(1).

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3.8	Waiver Request(s).....	4
3.9	Recommendations	4
3.10	Comments for Other OGD Disciplines	5
4	Appendix	6
4.1	Formulation Data	6
4.2	Outcome Page	8

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Benztropine Mesylate Injection USP, 1 mg/mL as 2 mL Vials
Reference Product	Cogentin® (Benztropin Mesylate) Injection, 1 mg/mL as 2 mL Vials
RLD Manufacturer	Ovation Pharmaceuticals Inc.
NDA No.	12-051
RLD Approval Date	December 21, 1959
Indication	For use as an adjunct in the therapy of all forms of parkinsonism. Useful also in the control of extrapyramidal disorders (except tardive dyskinesia) due to neuroleptic drugs (e.g., phenothiazines).

3.2 PK/PD Information¹

Bioavailability	Benztropine is administered orally and parenterally. It is absorbed from the GI tract, crosses the blood-brain barrier, and may cross the placenta. After oral administration, a small part of the dose may pass through the GI tract unchanged into the feces.
Food Effect	N/A for IV product
Tmax	N/A for IV product
Metabolism	Benztropine's metabolism is unknown.
Excretion	The drug is excreted renally, both as parent drug and as metabolites
Half-life	N/A
Drug Specific Issues (if any)	Safety use in pregnancy has not been established. Benztropine mesylate may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations:	There are no relevant control documents available. No ANDAs have been approved for the injection dosage form of Benztropine Mesylate.
Summary of OGD or DBE History:	090287 (Hikma Pharmaceutical, 12/27/2007, pending) (b) (4) Withdrawn, Unapproved . Withdrawn, Unapproved Withdrawn, Unapproved

¹ <http://www.clinicalpharmacology-ip.com>

3.4 Contents of Submission

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

3.5 Pre-Study Bioanalytical Method Validation

N/A

3.6 In Vivo Studies

N/A

3.7 Formulation

Location in appendix	Section 4.11, 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?	FORMULATION ACCEPTABLE
If not acceptable, why?	

3.8 Waiver Request(s)

Strengths for which waivers are requested	1 mg/mL
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	WAIVERS GRANTED
If not then why?	

3.9 Recommendations

1. The Division of Bioequivalence deems that the test product, Benztropine Mesylate Injection USP, 1mg/mL is bioequivalent to the reference product, Cogentin® 1mg/mL, manufactured by Ovation Pharmaceuticals.

2. Pursuant to 21 CFR §320.22 (b)(1), the waiver of *in vivo* bioequivalence study requirements for the test product Benztropine Mesylate Injection USP, 1mg/ml is **granted**.

3.10 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Formulation Data

Ingredient	Nexus' Benztropine Mesylate Injection, USP, 1 mg/mL ²	Ovation's Cogentin® Injection, 1 mg/mL	Function Type
	Amount (mg/mL)	Amount (mg/mL)	
Benzotropine Mesylate, USP	1	1	Active Ingredient
Sodium Chloride, USP	9	9	Tonicity Agent
Water for Injection, USP	QS	QS	Drug Product Vehicle

Reference Listed Product (as per COMIS):

N012015 PRODUCT DETAILS			
Prod:001	TE:	Rx/OTC:RX	Trade:COGENTIN
Received 08-JUN-1959	Approval APPEF/21-DEC-1959	Discontinued	Withdrawal
Current	Dosage Form(s) INJECTION	Route(s) of Administration IM - IV	
Part 01			
Ingredient Name	POTENCY	Type	
BENZTROPINE MESYLATE	1MG/ML	ACTIVE	
SODIUM CHLORIDE	9MG/ML	INACTIVE	
WATER FOR INJECTION, STERILE	QUANTITY SUFFICIENT	INACTIVE	

Reviewer's comments:

The formulation of the test product is Q1 and Q2 identical with the reference listed product.

All excipients are compendial grade. The excipient levels do not exceed the IIG.

² Nexus' drug product summary Table 2.3.P.1.a.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-233
APPLICANT: Nexus Pharmaceuticals Inc.
DRUG PRODUCT: Benztropine Mesylate Injection, USP
1 mg/mL

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

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}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.2 Outcome Page

ANDA: 90-233

Enter Review Productivity and Generate Report

Reviewer: Zhao, Joan

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Benztropine Mesylate Injection, USP 1 mg/mL vials

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
6470	12/14/2007	Other	Waiver Injectable	1	1
				Bean Total:	1

DBE2 Complexity Points

Waiver Application

Injection Waiver	1
Grand Total Productivity Points	1

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

/s/

Joan Zhao
9/18/2008 09:52:00 AM
BIOPHARMACEUTICS

Paul Seo
9/18/2008 02:22:30 PM
BIOPHARMACEUTICS

Moheb H. Makary
9/18/2008 04:02:38 PM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of
Bioequivalence II

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-223

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

January 21, 2009

ANDA: 90-233

Drug Product Name

Proprietary: N/A

Non-proprietary: Benztropine Mesylate Injection

Drug Product Priority Classification: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
12/14/2007	12/18/2007	N/A	10/29/2008

Submission History (for amendments only)

None

Applicant/Sponsor

Name: Nexus Pharmaceuticals, Inc.

Address: 430 N. Milwaukee Ave., Suite 9 Lincolnshire, IL 60069

Representative: Shahid Ahmed

Telephone: (847) 913-2720

Name of Reviewer: Eric K. Adeeku

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Original ANDA
 - 2. SUBMISSION PROVIDES FOR:** Initial marketing of the drug product
 - 3. MANUFACTURING SITE:**

(b) (4)
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Aqueous liquid, Parenteral, 1 mg/mL (2 mL fill in 2 cc vials), single dose.
 - 5. METHOD(S) OF STERILIZATION:**

(b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** N/A
- B. SUPPORTING/RELATED DOCUMENTS:**
 DMF

(b) (4)

 13 mm

(b) (4)

 coated rubber stoppers
- C. REMARKS:** None

filename: 90-233.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -** This submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the ‘Product Quality Microbiology Assessment’.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -** N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -** (b) (4)
- B. Brief Description of Microbiology Deficiencies -**
Validation data required for the depyrogenation of glass vials used to package the product. Data required for the validation of product endotoxin test method.
- C. Assessment of Risk Due to Microbiology Deficiencies -**
The safety risk associated with the microbiology deficiencies is considered high.

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Microbiologist: Eric Adeeku, Ph.D.
Microbiology Team Leader: Lynne Ensor, Ph.D.
- C. CC Block**
cc: Field Copy

Following this page, 13 pages withheld in full - (b)(4) Microbiology Review #1

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-233 APPLICANT: Nexus Pharmaceuticals, Inc.

DRUG PRODUCT: Bzntropine Mesylate Injection

Microbiology Deficiencies:

1.

(b) (4)

2.

3.

4.

Please clearly identify your amendment to this facsimile as “RESPONSE TO MICROBIOLOGY DEFICIENCIES”. The “RESPONSE TO MICROBIOLOGY DEFICIENCIES” should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Erik Adeeku
1/29/2009 01:44:28 PM
MICROBIOLOGIST

Bonnie McNeal
1/29/2009 04:00:22 PM
MICROBIOLOGIST
Checked for correct file and submission link. Both ok.

Lynne Ensor
2/2/2009 07:11:08 AM
MICROBIOLOGIST

Product Quality Microbiology Review

February 12, 2009

ANDA: 90-233

Drug Product Name

Proprietary: N/A

Non-proprietary: Benztropine Mesylate Injection

Drug Product Priority Classification: N/A

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
02/12/2009	02/17/2009	N/A	02/12/2009
02/18/2009	02/19/2009	N/A	02/18/2009

Submission History (for amendments only)

Date(s) of previous submission(s)	Microbiology Review #	Date(s) of previous Micro Review(s)
12/14/2007	1	02/23/2009

Applicant/Sponsor

Name: Nexus Pharmaceuticals, Inc.

Address: 430 N. Milwaukee Ave., Suite 9 Lincolnshire, IL 60069

Representative: Shahid Ahmed

Telephone: (847) 913-2720

Name of Reviewer: Eric K. Adeeku

Conclusion: **Recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUBMISSION:** Original ANDA

 2. **SUBMISSION PROVIDES FOR:** Initial marketing of the drug product

 3. **MANUFACTURING SITE:**

(b) (4)

 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Aqueous liquid, Parenteral, 1 mg/mL (2 mL fill in 2 cc vials), single dose.

 5. **METHOD(S) OF STERILIZATION:**

(b) (4)

 6. **PHARMACOLOGICAL CATEGORY:** N/A
- B. SUPPORTING/RELATED DOCUMENTS:**
 DMF

(b) (4)

 13 mm

(b) (4)

 coated rubber stoppers
- C. REMARKS:**
 The subject amendment provides responses to the microbiology deficiencies conveyed to the applicant in the Agency's February 02, 2009 deficiency letter.
- Further information submitted by Mr. Shahid Ahmed following a teleconference on February 11, 2009.

filename: 90-233a1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - This submission is recommended for approval on the basis of sterility assurance.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** - N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - (b) (4)
- B. Brief Description of Microbiology Deficiencies** - None identified.
- C. Assessment of Risk Due to Microbiology Deficiencies** - No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Microbiologist: Eric Adeeku, Ph.D.
Microbiology Team Leader: Lynne Ensor, Ph.D.
- C. CC Block**
cc: Field Copy

Following this page, 3 pages withheld in full - (b)(4) Microbiology Review #2

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/s/

Erik Adeeku
2/25/2009 10:26:56 AM
MICROBIOLOGIST

Mark Anderson
2/25/2009 11:44:18 AM
MICROBIOLOGIST

checked for correct file and linking; all OK

Lynne Ensor
2/25/2009 11:48:51 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 90-223

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



ANDA 90-233

Nexus Pharmaceuticals, Inc.
Attention: Shahid Ahmed
430 N. Milwaukee Avenue
Suite 9
Lincolnshire, IL 60069

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 14, 2007, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Benztropine Mesylate Injection, 1 mg/mL, 2 mL vials.

Reference is also made to the telephone conversation dated April 7, 2008 and your correspondence dated April 7, 2008.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d) (3) for the following reasons:

The Drug Master File (DMF) information submitted to the agency was incomplete; hence the review cannot be completed. Please submit the following:

- Batch Records for the Active Pharmaceutical Ingredient (API)
- Description of Synthesis with Flow Chart
- Stability data for the API
- Yield and ranges of the API

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please provide the following:

- Please provide a side-by-side comparison of the proposed package labeling to the reference listed drug with the differences annotated and explained.
- Please cite the functions of each testing facility

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Rebekah Granger
Project Manager
(240) 276-8439

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Martin Shimer
4/24/2008 02:35:33 PM
Signing for Wm Peter Rickman



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-233

Nexus Pharmaceuticals Inc.
Attention: Shahid Ahmed
430 N. Milwaukee Avenue
Suite 9
Lincolnshire, IL 60069

Dear Sir:

After careful review, the Office of Generic Drugs has decided to rescind our "Refuse to Receive" letter dated April 24, 2008. Accordingly, the application is acceptable for filing.

Reference is also made to your correspondence dated April 7 and May 2, 2008.

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

NAME OF DRUG: Benztropine Mesylate Injection USP, 1 mg/mL, 2 mL vials

DATE OF APPLICATION: December 14, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 18, 2007

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

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

Should you have questions concerning this application, contact:

Theresa Liu
Project Manager
240-276-8555

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Martin Shimer
7/8/2008 08:48:24 AM
Signing for Wm Peter Rickman

COMPLETE RESPONSE -- MINOR

ANDA 90-233

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: Nexus Pharmaceuticals Inc.

TEL: 847-913-2720

ATTN: Shahid Ahmed

FAX: 847-913-2721

FROM: Theresa Liu

FDA CONTACT PHONE: (240) 276-8555

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 14, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Benztropine Mesylate Injection USP, 1 mg/mL (2 mg/2 mL).

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 (3 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.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

Following this page, 1 page withheld in full

6.

7.

8.

9.

B. Comments:

1. The labeling, and Microbiology portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.
2. Please be aware that the application cannot be approved until deficiencies regarding drug substance have been addressed satisfactorily by the (b) (4).
3. Please provide updated stability data for the exhibit batch.

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/

Damaris Maldonado
9/26/2008 10:15:51 AM

October 6, 2008

Florence S. Fang,
Director,
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855

Chemistry Minor Amendment

**Reference: ANDA 90-233 Benzotropine Mesylate Injection, USP
1 mg/mL, 2mL fill in 2cc Vial**

Dear Ms. Fang:

This letter is in response to the Minor Amendment dated September 26, 2008 concerning Nexus Pharmaceuticals Inc., pending ANDA for Benzotropine Mesylate Injection, USP submitted on December 14, 2007.

Following are the responses to the deficiencies cited in the Minor Amendment concerning this application.

FDA form 356h is provided in [Attachment 1](#).

A.

1.

(b) (4)

2.

3.

Following this page, 4 pages withheld in full - (b)(4)

We acknowledge the Agency's comments and will wait to receive communication from OGD.

- 2. Please be aware that the application cannot be approved until deficiencies regarding drug substance have been addressed satisfactorily by the (b) (4)**

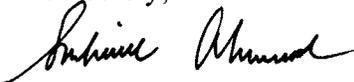
(b) (4) has provided appropriate information concerning the Benztropine Mesylate drug substance and we hope that all the issues have been addressed to the Agency's satisfaction.

- 3. Please provide updated stability data for the exhibit batch.**

The updated stability data for the exhibit batch is provided in Attachment 9.

We hope that the provided information is to your satisfaction. However, if you need any additional information than please contact the undersigned at your convenience.

Sincerely,



Shahid Ahmed
Co-President

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (240-276-8408)



TO: Shahid Ahmed	FROM: Bonnie McNeal
Nexus Pharmaceuticals Inc.	Microbiology Project Manager
PHONE: 847-913-2720	PHONE: (240) 276-8831
FAX: 847-913-2721	FAX: (240) 276-8725

Total number of pages, excluding this cover sheet: 2

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.

This will improve document availability to review staff.

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for ANDA 90-233 for Benztropine Mesylate Injection USP. The submission reviewed was submitted on December 14, 2007. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication 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-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Bonnie McNeal or Mark Anderson.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-233 APPLICANT: Nexus Pharmaceuticals, Inc.

DRUG PRODUCT: Bzotropine Mesylate Injection USP

Microbiology Deficiencies:

1.

(b) (4)

2.

3.

4.

Please clearly identify your amendment to this facsimile as “RESPONSE TO MICROBIOLOGY DEFICIENCIES”. The “RESPONSE TO MICROBIOLOGY DEFICIENCIES” should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Lynne Ensor
2/2/2009 07:11:32 AM



NEXUS PHARMACEUTICALS, INC.

February 5, 2009

Lynne A. Ensor, Ph.D
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855

Microbiology Minor Amendment Response

**Reference: ANDA 90-233 Bzotropine Mesylate Injection, USP
1 mg/mL, 2mL fill in 2cc Vial**

Dear Dr. Ensor:

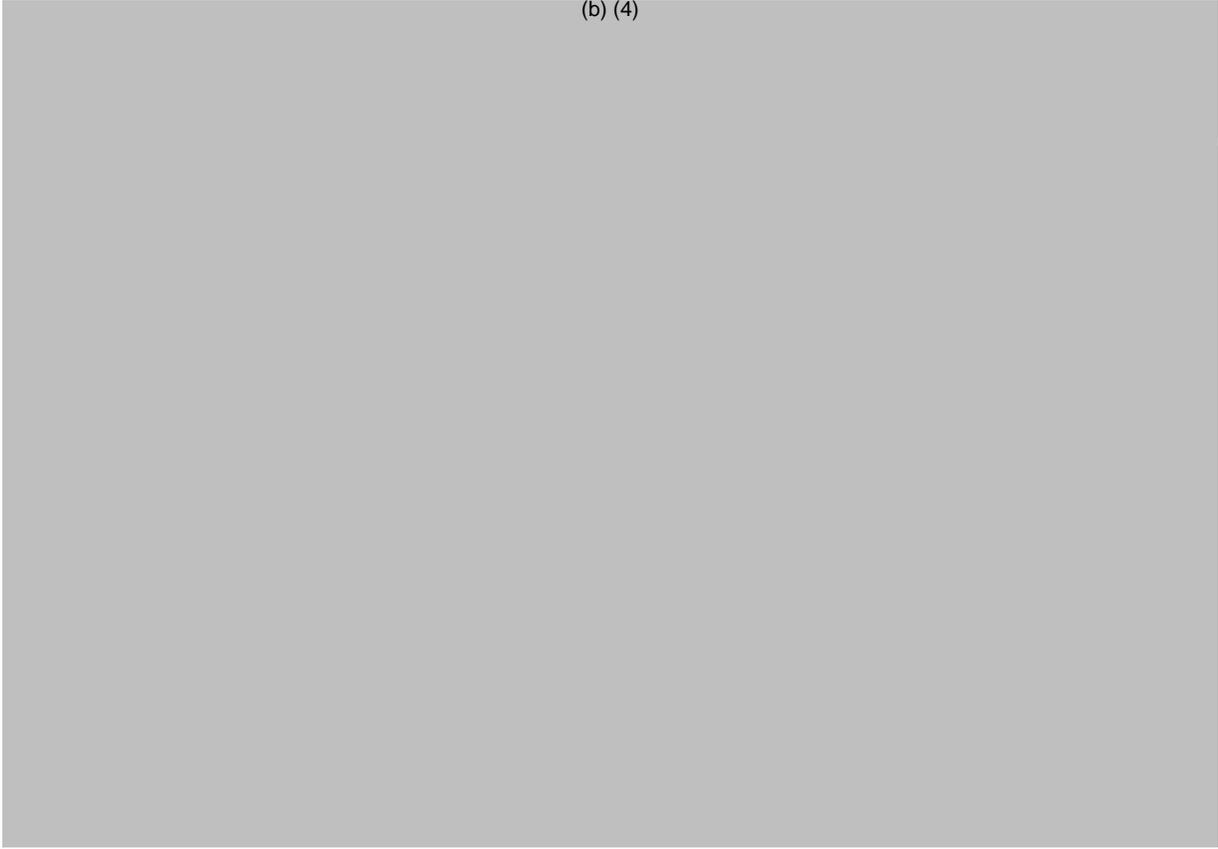
This letter is in response to the Minor Amendment dated February 2, 2009 concerning Nexus Pharmaceuticals Inc., pending ANDA for Bzotropine Mesylate Injection, USP submitted on December 14, 2007.

Following are the responses to the deficiencies cited in the Minor Amendment concerning this application.

FDA form 356h is provided in **Attachment 1**.

1.

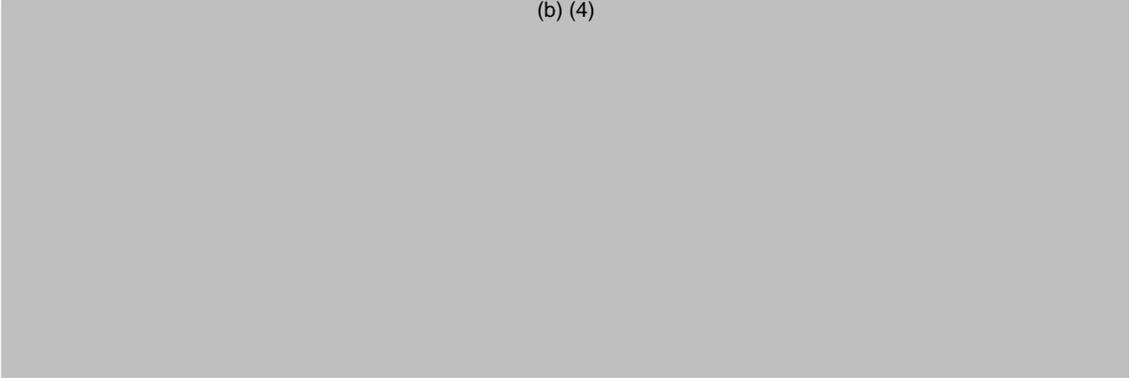
(b) (4)



430 N. Milwaukee Ave., Suite 9 • Lincolnshire, IL 60069
(847) 913 2720 (phone) (847) 913-2721(fax)

Following this page, 3 pages withheld in full - (b)(4)

(b) (4)



We hope that the provided information is to your satisfaction. However, if you need any additional information than please contact the undersigned at your convenience.

Sincerely,



Shahid Ahmed
Co-President



NEXUS PHARMACEUTICALS, INC.

February 11, 2009

Eric K. Adeeku, Ph.D
Review Microbiologist
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855

Microbiology Minor Amendment Response

**Reference: ANDA 90-233 Bzntropine Mesylate Injection, USP
1 mg/mL, 2mL fill in 2ccVials**

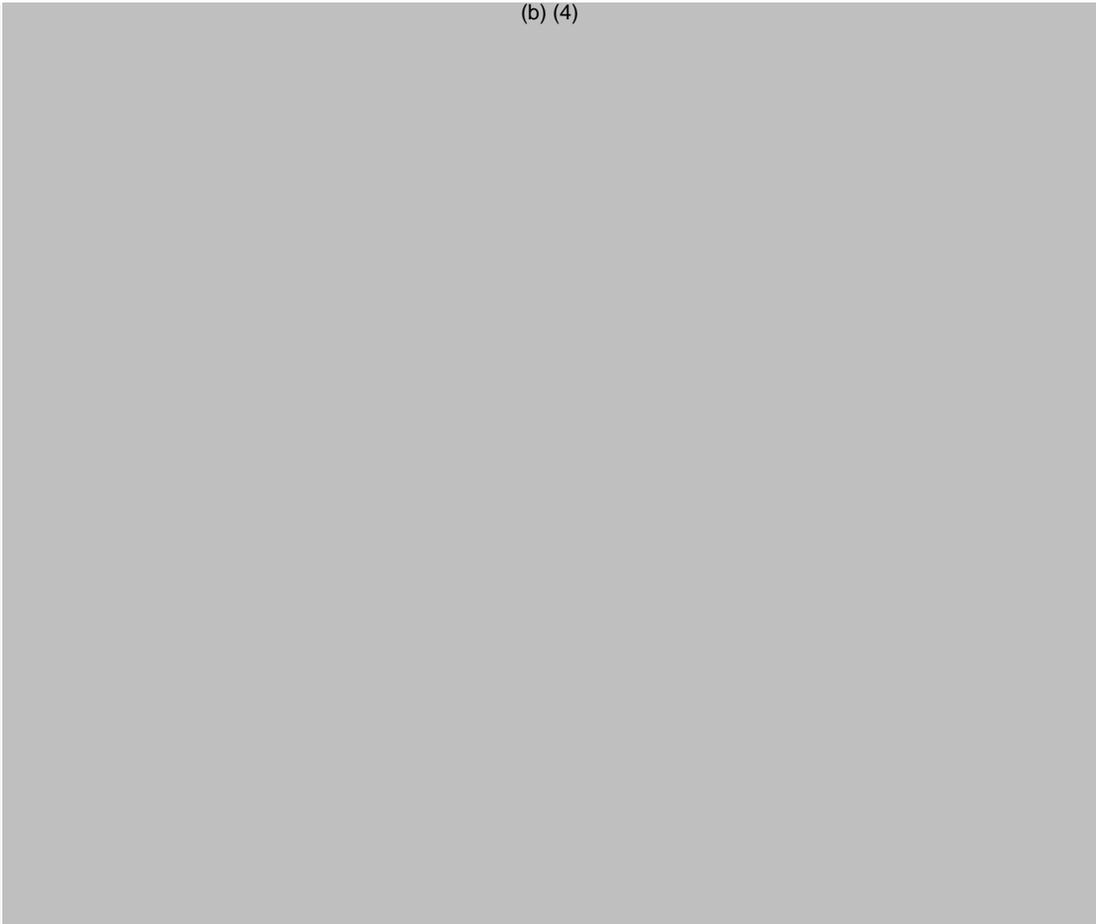
Dear Dr. Adeeku:

This letter is in response to the facsimile dated February 11, 2009 as well as our phone conversation concerning Nexus Pharmaceuticals Inc., unapproved ANDA for Bzntropine Mesylate Injection, USP submitted on December 14, 2007. Following are the responses to the deficiencies cited in the Minor Amendment concerning this application.

FDA form 356h is provided.

1.

(b) (4)



(b) (4)

2.

We hope that the provided information is to your satisfaction. However, if you need any additional information than please contact the undersigned at your convenience.

Sincerely,



Shahid Ahmed
Co-President



NEXUS PHARMACEUTICALS, INC.

May 6, 2009

LABELING AMENDMENT

Soojung Sarah Park
Division of Labeling & Program Support
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Reference: ANDA 90-233 Bzotropine Mesylate Injection, USP 0.1%

Dear Ms. Park:

This letter is in response to the Labeling Amendment dated March 31, 2009 concerning the draft labeling for our unapproved ANDA for Bzotropine Mesylate Injection, USP.

Attached is FDA form 356h.

Per your request enclosed is a CD that contains the FPLs for the Container, Carton and Package Insert as well as the annotated Labeling as Pdf files. All the electronic files are virus free and have been checked using Norton 360 version 3 software.

The alphabets before the arrows present in the annotated FPL Labels represent the Agency's proposed changes mentioned in the Labeling Amendment dated march 31, 2009.

Should you have any questions or require additional information concerning this amendment, than please contact me at (847) 913-2720 (phone) or (847)-913-2721 (fax) at your convenience.

Sincerely,

Shahid Ahmed
Co-President



NEXUS PHARMACEUTICALS, INC.

July, 20 2009

Theresa Liu, Pharm.D
Project Manager
Division of Chemistry II, Team 7
Office of Generic Drugs
Center for Drug Evaluation and Research
7500 Standish Place
Rockville, MD 20855

Telephone Amendment

**Reference: ANDA 90-233 Bzotropine Mesylate Injection, USP
1 mg/mL, 2mL fill in 2ccVial**

Dear Ms. Liu:

This letter is in response to your voice mail today concerning the Bzotropine Mesylate Injection, USP application review update as well as (b) (4) Testing Laboratory.

Based on the current compliance status of (b) (4) Testing Group, we would like to inform the Agency that Nexus Pharmaceuticals is withdrawing use of the (b) (4) Testing Group to perform USP IR-ID Test, Melting Point, Residue on Ignition and Heavy Metals analysis for commercial lots of Bzotropine Mesylate, USP API.

Nexus Pharmaceuticals Inc., will instead employ (b) (4) Laboratory group to perform the USP tests listed in Bzotropine Mesylate USP monograph since (b) (4) Laboratory group has been listed in the original ANDA as an outside analytical testing Laboratory for performing USP <788> (Particulate Matter) testing for the proposed drug product.

However, if you require any additional information concerning this application than please contact me at your convenience.

Sincerely,

Shahid Ahmed
Co-President

OGD APPROVAL ROUTING SUMMARY

ANDA # 90-233 Applicant Nexus Pharmaceuticals, Inc.
Drug Benzotropine Mesylate Injection USP Strength(s) 1 mg/mL

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. **Martin Shimer**
Chief, Reg. Support Branch
Date 9 July 2009 Initials SMHS
Date 7/20/09 Initials rlw
Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Cogentin NDA# 12-015
Patent/Exclusivity Certification: Yes No Date Checked N/A
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 12/18/2007, BOS=Cogentin NDA 12-015, PI certification provided. ANDA ack for filing on 12/18/2007 (LO dated 7/8/2008-ANDA originally RTR'd and this RTR was later rescinded). There are no unexpired patents or exclusivities which protect the RLD. ANDA is eligible for immediate Full Approval.

2. **Project Manager, Theresa Liu Team 7**
Review Support Branch
Date 7/2/09 Initials stcl
Date _____ Initials _____
Original Rec'd date 12/14/07 EER Status Pending Acceptable OAI
Date Acceptable for Filing 12/18/07 Date of EER Status 6/18/09
Patent Certification (type) PI Date of Office Bio Review 9/25/08
Date Patent/Exclus. expires Date of Labeling Approv. Sum 7/1/09
Citizens' Petition/Legal Case Yes No Labeling Acceptable Email Rec'd Yes No
(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes No
First Generic Yes No Date of Sterility Assur. App. 2/25/09
Priority Approval Yes No Methods Val. Samples Pending Yes No
(If yes, prepare Draft Press Release, Email MV Commitment Rcd. from Firm Yes No
it to Cecelia Parise) Modified-release dosage form: Yes No
Acceptable Bio reviews tabbed Yes No Interim Dissol. Specs in AP Ltr: Yes
Bio Review Filed in DFS: Yes No
Suitability Petition/Pediatric Waiver Yes
Pediatric Waiver Request Accepted Rejected Pending
Previously reviewed and tentatively approved Date _____
Previously reviewed and CGMP def. /NA Minor issued Date _____
Comments:

3. **Labeling Endorsement**
Reviewer: Labeling Team Leader:
Date July 10, 2009 Date July 10, 2009
Name/Initials Koung Lee/KL for S. Park Name/Initials Koung Lee/KL
Comments:
Hi Theresa,

I concur and also concur on behalf of Sarah.

Thanks.

Koung

4. **David Read (PP IVs Only)** Pre-MMA Language included Date _____
OGD Regulatory Counsel, Post-MMA Language Included Initials _____
Comments:

5. **Div. Dir./Deputy Dir.** Date 7/15/09
Chemistry Div. II Initials RCA

Comments: CMC OK, see attached spreadsheets. Alkylsulfonates well controlled.

6. **Frank Holcombe** First Generics Only Date 7/24/09
Assoc. Dir. For Chemistry Initials RRR
Comments: (First generic drug review)
CMC ok; for Frank,

7. Vacant Date _____
Deputy Dir., DLPS Initials _____

8. **Peter Rickman** Date 7/28/2009
Director, DLPS Initials swpr
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Comments: ANDA submitted on 12/18/2007, BOS=Cogentin NDA 12-015, applicant made a PI patent certification. ANDA ack for filing on 12/18/2007; ANDA originally RTR'd and this RTR was later rescinded. There are no unexpired patents or exclusivities which protect the RLD. Labeling acceptable 7/1/2009 per AP Summary; Bio acceptable 9/18/2008 (waiver granted); EER acceptable 6/18/2009; ANDA is eligible for Full Approval.

OR

8. **Robert L. West** Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes No ; Pending Legal Action: Yes No ; Petition: Yes No
Press Release Acceptable
Comments:

9. **Gary Buehler** Date _____
Director, OGD Initials _____
Comments:
First Generic Approval PD or Clinical for BE Special Scientific or Reg.Issue
Press Release Acceptable

10. Project Manager, Theresa Liu Team 7 Date 7/28/09
Review Support Branch Initials tcl
_____ Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:30 PM Time notified of approval by phone 3:30 PM Time approval letter faxed
FDA Notification:
7/28/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
7/28/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- ANDA 90233	----- ORIG 1	----- NEXUS PHARMACEUTICA LS INC	----- BENZTROPINE MESYLATE

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/s/

THERESA C LIU
07/31/2009