# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number 40184**

**Trade Name Trihexyphenidyl Hydrochloride Tablets USP 2mg and 5mg**

**Generic Name Trihexyphenidyl Hydrochloride Tablets 2mg and 5mg**

**Sponsor Circa Pharmaceuticals, Inc.**

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 40184**

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| | Included | Pending Completion | Not Prepared | Not Required |
|---|---|---|---|---|
| **Approval Letter** | X | | | |
| **Tenative Approval Letter** | | | | |
| **Approvable Letter** | | | | |
| **Final Printed Labeling** | X | | | |
| **Medical Review(s)** | | | | |
| **Chemistry Review(s)** | X | | | |
| **EA/FONSI** | | | | |
| **Pharmacology Review(s)** | | | | |
| **Statistical Review(s)** | | | | |
| **Microbiology Review(s)** | | | | |
| **Clinical Pharmacology Biopharmaceutics Review(s)** | | | | |
| **Bioequivalence Review(s)** | X | | | |
| **Administrative Document(s)** | X | | | |
| **Correspondence** | X | | | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 40184**

## APPROVAL LETTER

ANDA 40-184

FEB 6 1998

Circa Pharmaceuticals, Inc.
Attention: Joyce Anne DelGaudio
P.O. Box 30
33 Ralph Ave.
Copiague, NY 11726-0030

Dear Madam:

This is in reference to your abbreviated new drug application dated March 26, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Trihexyphenidyl Hydrochloride Tablets USP, 2 mg and 5 mg.

Reference is also made to your amendment dated April 4, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Trihexyphenidyl Hydrochloride Tablets USP, 2 mg and 5 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Artane Tablets 2 mg and 5 mg, respectively, of Lederle Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

2/6/98

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 40184

## FINAL PRINTED LABELING

NDC 52544-576-10

**Trihexyphenidyl Hydrochloride Tablets, USP**

**5 mg**

WATSON LABORATORIES, INC.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

**1000 Tablets**

**Each tablet contains:**
Trihexyphenidyl HCl, USP ..... 5 mg

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP.

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

**USUAL DOSAGE:** SEE PACKAGE INSERT.

10220
R1 2/97

**Manufactured by:**
Watson Laboratories, Inc.
Copiague, NY 11726

N 3 52544-576-10 8

Lot No.:
Exp. Date:

NDC 52544-576-01

**Trihexyphenidyl Hydrochloride Tablets, USP**

**5 mg**

WATSON LABORATORIES, INC.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

**100 Tablets**

**Each tablet contains:**
Trihexyphenidyl HCl, USP ..... 5 mg

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP.

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

**USUAL DOSAGE:** SEE PACKAGE INSERT.

10210
R1 2/97

**Manufactured by:**
Watson Laboratories, Inc.
Copiague, NY 11726

N 3 52544-576-01 6

Lot No.:
Exp. Date:

NDC 52544-575-10

**Trihexyphenidyl Hydrochloride Tablets, USP**

**2 mg**

WATSON LABORATORIES, INC.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

**1000 Tablets**

**Each tablet contains:**
Trihexyphenidyl HCl, USP ..... 2 mg

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP.

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

**USUAL DOSAGE:** SEE PACKAGE INSERT.

10200
R1 2/97

**Manufactured by:**
Watson Laboratories, Inc.
Copiague, NY 11726

N 3 52544-575-10 1

Lot No.:
Exp. Date:

NDC 52544-575-01

**Trihexyphenidyl Hydrochloride Tablets, USP**

**2 mg**

WATSON LABORATORIES, INC.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

**100 Tablets**

**Each tablet contains:**
Trihexyphenidyl HCl, USP ..... 2 mg

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP.

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

**USUAL DOSAGE:** SEE PACKAGE INSERT.

10190
R1 2/97

**Manufactured by:**
Watson Laboratories, Inc.
Copiague, NY 11726

N 3 52544-575-01 9

Lot No.:
Exp. Date:

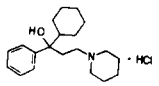
# TRIHEXYPHENIDYL HYDROCHLORIDE TABLETS, USP

**DESCRIPTION**

Trihexyphenidyl HCl is a synthetic antispasmodic. Each tablet, for oral administration, contains 2 mg or 5 mg trihexyphenidyl HCl and the following inactive ingredients: Dibasic Calcium Phosphate Dihydrate, Magnesium Stearate, Microcrystalline Cellulose, and Stearic Acid.

Trihexyphenidyl HCl is a white or slightly off-white, crystalline powder, having not more than a very faint odor.

Trihexyphenidyl HCl is the substituted piperidine salt, (±)-α-Cyclohexyl-α-phenyl-1-piperidinepropanol hydrochloride. Its molecular formula is $C_{20}H_{31}NO$·HCl. The structural formula is:




**CLINICAL PHARMACOLOGY**

Trihexyphenidyl HCl exerts a direct inhibitory effect upon the parasympathetic nervous system. It also has a relaxing effect on smooth musculature; exerted both directly upon the muscle tissue itself and indirectly through an inhibitory effect upon the parasympathetic nervous system. Its therapeutic properties are similar to those of atropine, although undesirable side effects are ordinarily less frequent and severe than with the latter.

**INDICATIONS AND USAGE**

Trihexyphenidyl HCl tablets are indicated as an adjunct in the treatment of all forms of parkinsonism (postencephalitic, arteriosclerotic and idiopathic). It is often useful as adjuvant therapy when treating these forms of parkinsonism with levodopa. Additionally, it is indicated for the control of extrapyramidal disorders caused by central nervous system drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes, and butyrophenones.

**WARNINGS**

Patients to be treated with trihexyphenidyl HCl should have a gonioscope evaluation and close monitoring of intraocular pressures at regular periodic intervals.

**PRECAUTIONS**

Although trihexyphenidyl HCl is not contraindicated for patients with cardiac, liver, or kidney disorders, or with hypertension, such patients should be maintained under close observation.

Since the use of trihexyphenidyl HCl may in some cases continue indefinitely and since it has atropine-like properties, patients should be subjected to constant and careful long-term observation to avoid allergic and other untoward reactions. Inasmuch as trihexyphenidyl HCl possesses some parasympatholytic activity, it should be used with caution in patients with glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostatic hypertrophy. Geriatric patients, particularly over the age of 60, frequently develop increased sensitivity to the actions of drugs of this type, and hence, require strict dosage reg-

benzodiazepines, phenothiazines, thioxanthenes, and butyrophenones.

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Tardive dyskinesia may appear in some patients on long-term therapy with antipsychotic drugs 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. However, parkinsonism and tardive dyskinesia often coexist in patients receiving chronic neuroleptic treatment, and anticholinergic therapy with trihexyphenidyl HCl may relieve some of these parkinsonism symptoms.

**ADVERSE REACTIONS**

Minor side effects, such as dryness of the mouth, blurring of vision, dizziness, mild nausea or nervousness, will be experienced by 30 to 50 percent of all patients. These sensations, however, are much less troublesome with trihexyphenidyl HCl than with belladonna alkaloids and are usually less disturbing than unalleviated parkinsonism. Such reactions tend to become less pronounced, and even to disappear, as treatment continues. Even before these reactions have remitted spontaneously, they may often be controlled by careful adjustment of dosage form, amount of drug, or interval between doses.

Isolated instances of suppurative parotitis secondary to excessive dryness of the mouth, skin rashes, dilatation of the colon, paralytic ileus, and certain psychiatric manifestations such as delusions and hallucinations, plus one doubtful case of paresis all of which may occur with any of the atropine-like drugs, have been reported rarely with trihexyphenidyl HCl.

Patients with arteriosclerosis or with a history of idiosyncrasy to other drugs may exhibit reactions of mental confusion, agitation, disturbed behavior, or nausea and vomiting. Such patients should be allowed to develop a tolerance through the initial administration of a small dose and gradual increase in dose until an effective level is reached. If a severe reaction should occur, administration of the drug should be discontinued for a few days and then resumed at a lower dosage. Psychiatric disturbances can result from indiscriminate use (leading to overdosage) to sustain continued euphoria

Potential side effects associated with the use of any atropine-like drugs include constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intraocular tension, weakness, vomiting, and headache.

The occurrence of angle-closure glaucoma due to long-term treatment with trihexyphenidyl HCl has been reported.

**DOSAGE AND ADMINISTRATION**

Dosage should be individualized. The initial dose should be low and then increased gradually, especially in patients over 60 years of age. Whether trihexyphenidyl HCl may best be given before or after meals should be determined by the way the patient reacts. Postencephalitic patients, who are usually more prone to excessive salivation, may prefer to take it after meals and may, in addition, require small amounts of atropine which, under such circumstances, is sometimes an effective adjuvant. If trihexyphenidyl HCl tends to dry the mouth excessively, it may be better to take it before meals, unless it causes nausea. If taken after meals, the thirst sometimes induced can be allayed by mint candies, chewing gum or water.

**Trihexyphenidyl HCl in Idiopathic Parkinsonism:** As initial therapy for parkinsonism, 1 mg of trihexyphenidyl HCl in tablet form may be administered the first day. The dose may then be increased by 2 mg increments at intervals of 3 to 5 days, until a total of 6 to 10 mg is given daily. The total daily dose will depend upon what is found to be the optimal level. Many patients derive maximum benefit from this daily total of 6 to 10 mg, but some patients, chiefly those in the postencephalitic group, may require a total daily dose of 12 to 15 mg.

**Trihexyphenidyl HCl in Drug-Induced Parkinsonism:** The size and frequency of dose of trihexyphenidyl HCl needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines, thioxanthenes, and butyrophenones, must be determined empirically. The total daily dosage usually ranges between 5 and 15 mg-although, in some cases, these reactions have been satisfactorily controlled on as little as 1 mg daily, it may be advisable to commence therapy with a single 1 mg dose. If the extrapyramidal manifestations are not controlled in a few hours, the subsequent doses may be progressively increased until satisfactory control is achieved. Satisfactory control may sometimes be more rapidly achieved by temporarily reducing the dosage of the tranquilizer on instituting trihexyphenidyl HCl therapy and then adjusting dosage of both drugs until the desired ataractic effect is retained without onset of extrapyramidal reactions.

It is sometimes possible to maintain the patient on a reduced trihexyphenidyl HCl dosage after the reactions have remained under control for several days. Instances have been reported in which these reactions have remained in remission for long periods after trihexyphenidyl HCl therapy was discontinued.

**Concomitant Use of Trihexyphenidyl HCl with Levodopa:** When trihexyphenidyl HCl is used concomitantly with levodopa, the usual dose of each may need to be reduced. Careful adjustment is necessary, depending on side effects and degree of symptom control. Trihexyphenidyl HCl dosage of 3 to 6 mg daily, in divided doses, is usually adequate.

**Concomitant Use of Trihexyphenidyl HCl with Other Parasympathetic Inhibitors:** Trihexyphenidyl HCl may be substituted, in whole or in part, for other parasympathetic inhibitors. The usual technique is partial substitution initially, with progressive reduction in the other medication as the dose of trihexyphenidyl HCl is increased.

Trihexyphenidyl HCl Tablets - The total daily intake of trihexyphenidyl HCl tablets is tolerated best if divided into three doses and taken at mealtimes. High doses (>10 mg daily) may be divided into four parts, with three doses administered at mealtimes and the fourth at bedtime.

**HOW SUPPLIED**

Trihexyphenidyl HCl Tablets are available as follows:

2 mg: White, round, scored tablets debossed with "575 and Watson" on one

the postencephalitic group, may require a total daily dose of 12 to 15 mg.

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**HOW SUPPLIED**

Trihexyphenidyl HCl Tablets are available as follows:

2 mg: White, round, scored tablets debossed with "575 and Watson" on one side and scored on the other side, in bottles of 100 (NDC 52544-575-01), and 1000 (NDC 52544-575-10).

5 mg: White, round scored tablets debossed with "576 and Watson" on one side and scored on the other side, in bottles of 100 (NDC 52544-576-01), and 1000 (NDC 52544-576-10).

Store at Controlled Room Temperature 15°-30°C (59°-86°F).

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP.

**CAUTION:** Federal Law Prohibits Dispensing Without Prescription.

**Manufactured By:**
Watson Laboratories, Inc.
Copiague, NY 11726

10180
R1 2/97

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 40184

## CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 2

2. ANDA **40-184**

3. NAME AND ADDRESS OF APPLICANT
Circa Pharmaceuticals, Inc.
33 Ralph Avenue
P.O. box 30
Copiague, NY 11726-0030

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Lederle's ARTANE® (NDA 06-773). Patent certification and exclusivity statement are provided (pp. 005-008).

**Final approval date is May 13, 1949.**

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
**Trihexyphenidyl HCl Tablets**

7. PROPRIETARY NAME
Artane®

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

| Firm | | FDA | |
|---|---|---|---|
| Orig. submission | 3/26/96 | Refused to file letter | 5/13/96 |
| Amendment | 6/5/96 | Phone conversation | 6/21/96 |
| | | Acknowledgment letter | 6/25/96 |
| | | CSO review | 4/22/96 |
| | | Labeling review | 8/05/96 |
| | | Bioequivalency | 9/13/96 |
| | | Deficiency letter | 12/5/96 |
| Amendment (Major) | 4/4/97 | Labeling review | 5/14/97 |

This review covers submission dated 4/4/97.

10. PHARMACOLOGICAL CATEGORY
*Anticholinergic/antiparkinsonian* - is indicated as an adjunct in the treatment of all forms of parkinsonism.

11. Rx or OTC
℞

12. RELATED DMF(s)

13. DOSAGE FORM
**Tablets (Oral)**

14. STRENGTH(S)
**2 mg and 5 mg**

15. CHEMICAL NAME AND STRUCTURE
1-Piperidinepropanol, α-cyclohexyl-α-phenyl-,hydochloride, (±)-.

$C_{20}H_{31}NO \cdot HCl$

Molecular weight: 337.94

**CAS-52-49-3**

***Drug substance and drug product are official USP 23 items.***

16. RECORDS AND REPORTS None

17. COMMENTS
    a. CMC deficiencies have been **satisfactory** addressed.
    b. Labeling is **satisfactory**, dated 5/14/97.
    c. Bio review is **satisfactory**, dated 9/13/96.
    d. found **adequate**, dated 4/10/97.
    e. Methods validation for drug substance and drug product **are not** required, both are compendia items.
    f. Establishment Evaluation Request **pending**.

18. CONCLUSIONS AND RECOMMENDATIONS

**APPROVE**

19. REVIEWER: Raymond Brown

DATE COMPLETED: August 15, 1997

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 40184

## BIOEQUIVALENCE REVIEW(S)

SEP 13 1996

Trihexyphenidyl HCl
2 mg and 5 mg Tablets
ANDA # 40-184
Reviewer: Moheb H. Makary
WP 40184D.396

Circa Pharmaceuticals , Inc.
Copiague, NY
Submission Date:
March 26, 1996

Review of Dissolution Data and Waiver Requests

I. Objective:

The firm requested waivers of bioequivalence study requirements for its test products Trihexyphenidyl HCl 2 mg and 5 mg Tablets and has submitted dissolution test results in support of its request. In July of 1995, Circa Pharmaceuticals, Inc., merged with Watson laboratories, Inc., of Corona California. One of the outcomes of this merger is the decision that all prescription drug products manufactured at either plant will be labeled as "Manufactured By" Watson Laboratories, Inc.

II. Formulations:

Circa's two formulas for Trihexyphenidyl HCl 2 mg and 5 mg Tablets are shown in Table I.

III. Dissolution Data:

The firm has submitted comparative dissolution data on its products Trihexyphenidyl HCl 2 mg and 5 mg Tablets and the listed reference drug products Artane® (Trihexyphenidyl HCl) 2 mg and 5 mg Tablets, manufactured by Lederle using the following dissolution conditions:

| | |
|---|---|
| Test products: | Watson's Trihexyphenidyl HCl<br>2 mg Tablets, lot #RD1126<br>5 mg Tablets, lot #RD1137 |
| Reference products: | Lederle's Artane®<br>2 mg Tablets, lot #350-410<br>5 mg Tablets, Lot #336-367 |
| Method: | USP 23, apparatus I (basket) at 100 rpm. |
| Medium: | 900 mL of acetate buffer pH 4.5 |
| Number of Tablets: | 12 |
| Specifications: | NLT in 45 minutes |

Dissolution testing results are shown in Table II.

IV. Comments:

1. Dissolution results for the test products Trihexyphenidyl HCl 2 mg and 5 mg Tablets are acceptable as summarized in Table II.

2. Trihexyphenidyl HCl 2 mg and 5 mg Tablets are coded AA in the Orange Book.

3. Waivers of bioequivalence study requirements for the test

products may be granted based on CFR 320.22 (c).

V. Recommendations:

1. The dissolution testing conducted by Circa Pharmaceuticals, Inc., on its Trihexyphenidyl HCl 2 mg and 5 mg Tablets, lot #RD1126 and RD1137, respectively, is acceptable. Waivers of *in vivo* bioequivalence study requirements for the test products are granted based on CFR 320.22 (c). From the bioequivalence point of view, the Division of Bioequivalence deems the Trihexyphenidyl HCl 2 mg and 5 mg Tablets to be bioequivalent to the reference products Artane® 2 mg and 5 mg Tablets, respectively, manufactured by Lederle.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of acetate buffer pH 4.5 at 37°C using USP 23 apparatus I (basket) at 100 rpm. The test products should meet the following specifications:

> Not less than 75% of the labeled amount of drug in the dosage form are dissolved in 45 minutes

The firm should be informed of the above recommendations.

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Date: 9/5/96

Concur: Date: 9/13/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MM/9-6-96/wp 40184D.396
cc: ANDA# 40-184 (original, duplicate), HFD-658 (Makary), Drug File, Division File.

**Table II. In Vitro Dissolution Testing**

Drug (Generic Name):Trihexyphenidyl HCl Tablets
Dose Strength: 2 mg and 5 mg
ANDA No.:40-184
Firm: Circa Pharmaceuticals Inc.
Submission Date: March 26, 1996
File Name:40184D.396

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 mL of acetate buffer pH 4.5
Specifications:NLT in 45 minutes
Reference Drug: Artane 2 mg and 5 mg Tablets
Assay Methodology

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot #RD1126 Strength(mg) 2 | | | Reference Product Lot #350-410 Strength(mg) 2 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 97.1 | | 2.1 | 99.2 | | 1.1 |
| 30 | 99.2 | | 1.5 | 100.1 | | 1.1 |
| 45 | 99.0 | | 1.7 | 100.2 | | 1.2 |
| 60 | 99.8 | | 1.2 | 102.0 | | 2.2 |
| | | | | | | |
| | | | | | | |

| Sampling Times (Minutes) | Test Product Lot #RD1137 Strength(mg) 5 | | | Reference Product Lot #336-367 Strength(mg) 5 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 96.7 | | 6.3 | 100.1 | | 2.8 |
| 30 | 101.4 | | 2.2 | 100.6 | | 2.4 |
| 45 | 102.3 | | 1.4 | 101.0 | | 2.6 |
| 60 | 103.3 | | 1.2 | 100.9 | | 2.6 |
| | | | | | | |

Table I



## VI. BIOAVAILABILITY/BIOEQUIVALENCE

### 5. Formulation Data (Comparison of all Strengths) and Regulatory Batch Information

Formula Comparison

Trihexyphenidyl HCl 2 mg Tablets
vs
Trihexyphenidyl HCl 5 mg Tablets

| COMPONENT NAME | 2 mg | w/w % | 5 mg | w/w % |
|---|---|---|---|---|
| Trihexyphenidyl HCl, USP | 2.10 * | 1.17 | 5.25 * | 1.75 |
| Microcrystalline Cellulose, NF | | | | |
| Dibasic Calcium Phosphate, USP Dihydrate | | | | |
| Stearic Acid, NF | | | | |
| Magnesium Stearate, NF | | | | |
| TOTAL TABLET WEIGHT | 180.10 | 100.0 | 300.25 | 100.0 |

* Contains 5.0% excess.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40184

CORRESPONDENCE

CIRCA PHARMACEUTICALS, INC.
33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

April 4, 1997

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
HFD-600, Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

**RE: TRIHEXYPHENIDYL HYDROCHLORIDE TABLETS, 2 MG & 5 MG;**
**ANDA 40-184**
**MAJOR AMENDMENT**

Dear Mr. Sporn:

We refer to the December 5, 1996 letter (copy enclosed) from the Division of Chemistry II providing comments on our Abbreviated New Drug Application dated March 26, 1996, submitted pursuant to Section 505(j) of the Food, Drug and Cosmetic Act for trihexyphenidyl hydrochloride tablets, 2 and 5 mg. We hereby submit this major amendment as a response to the December 5 deficiency letter. The following is an item-by-item response of the deficiencies.

**A. Chemistry Deficiencies:**

PAGES 2-8 REDACTED FOR CHEMISTRY - TRADE SECRET INFORMATION

RECEIVED

APR 07 1997

GENERIC DRUG

**B. Labeling Deficiencies**

*1. GENERAL COMMENT*

*Please be consistent throughout your labels and labeling regarding "Inc." in the manufacturers name.*

**Response:** We have revised our labels and labeling to assure that the "Manufactured By" designation is followed by the company name "Watson Laboratories, Inc.".

*2. CONTAINER - 100s and 1000s (2 mg and 5 mg)*

*a. We encourage the inclusion of "USP" in the established name.*

**Response:** We have revised our container labels to state Trihexyphenidyl Hydrochloride Tablets, USP, as the established name and trihexyphenidyl hydrochloride, USP, as the active pharmaceutical ingredient contained in each tablet.

*b. We encourage you to differentiate your different tablet strengths by the use of different colors, boxing, or some other means.*

**Response:** The recommendation listed above has been incorporated into our container labels. For purposes of differentiating the two strengths, the strength designation on the main panel of the 2 mg labels is printed in Process Blue, while it is printed in PMS Purple 513 for the 5 mg strength. Twelve copies of final printed container labels (six in the Archival Copy and six in the Review Copy) are enclosed under Attachment 8, as follows:

- Trihexyphenidyl Hydrochloride Tablets, 2 mg (100s)
- Trihexyphenidyl Hydrochloride Tablets, 2 mg (1000s)
- Trihexyphenidyl Hydrochloride Tablets, 5 mg (100s)
- Trihexyphenidyl Hydrochloride Tablets, 5 mg (1000s)

*3. INSERT*

*a. GENERAL COMMENT*

*Please be consistent throughout the text of the insert as to whether or not the "t" in "trihexyphenidyl" is capitalized.*

**Response:** The text of the insert has been revised so that the "t" in "trihexyphenidyl appears in the lower case, unless the word begins a sentence.

*b. TITLE*

*Revise the established name to read "Trihexyphenidyl Hydrochloride Tablets, USP". Note: We encourage the inclusion of "USP".*

*c. DESCRIPTION*

*i. Revise this section to read:*

*Trihexyphenidyl HCl is a synthetic antispasmodic. Each tablet, for oral administration, contains 2 mg or 5 mg trihexyphenidyl HCl and the following inactive ingredients: Dibasic ...*

*Trihexyphenidyl HCl is a white to slightly off-white, crystalline powder, having not more than a very faint odor.*

*Trihexyphenidyl HCl is the substituted piperidine salt, [insert the second chemical name found in the USP 23 monograph]. Its molecular formula is $C_{20}H_{31}NO \cdot HCl$. The structural formula is:*

*[insert structural formula as it appears in the USP 23 monograph]*

*d. ACTIONS*

*i. Revise this section heading to read "CLINICAL PHARMACOLOGY".*

*ii. Revise the first sentence to read:*

*Trihexyphenidyl HCl exerts a direct ...*

*e. INDICATIONS*

*i. Revise this section heading to read "INDICATIONS AND USAGE".*

*ii. Revise the first sentence to read:*

*Trihexyphenidyl HCl tablets are indicated ...*

*f. DOSAGE AND ADMINISTRATION*

*Trihexyphenidyl HCl in Idiopathic Parkinsonism, third sentence - ... found to be the optimal ...*

*g. HOW SUPPLIED*

*i. We encourage the inclusion of the "CAUTION: Federal Law ..." statement.*

*ii. Include the "Dispense in ..." statement that appears on your container labels.*

*h. Per 21 CFR 201.56(e), place the revision date prominently immediately following the last section of the insert.*

**Response:** We have revised our package insert according to your recommendations. Twelve copies of the final printed insert (six in the Archival Copy and six in the Review Copy) are enclosed under Attachment 8. Please note that immediately preceding the copies of final printed container labels and inserts, we have included a side-by-side labeling comparison with explanations of the annotated changes.

## FIELD COPY CERTIFICATION

Pursuant to 21 CFR 314.96(b), we certify that a field copy of this amendment has been sent by overnight courier to:

Mr. Alonzo Cruz, District Director
Food and Drug Administration (NYK-DO)
850 Third Avenue
Brooklyn, New York 11232-1593

We believe that this response adequately addresses each of the cited deficiencies. Should any additional information be required, please do not hesitate to contact us.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

Attachments

ANDA 40-184

Circa Pharmaceuticals, Inc.
Attention: Joyce Anne DelGaudio
33 Ralph Avenue
P.O. Box 30
Copiague, NY 11726-0030

DEC 5 1996

Dear Ms. DelGaudio:

This is in reference to your abbreviated new drug application dated March 26, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Trihexyphenidyl Hydrochloride Tablets USP, 2 mg and 5 mg.

Reference is also made to your amendment dated June 5, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

1. GENERAL COMMENT

Please be consistent throughout your labels and labeling regarding "Inc." in the manufacturer's name.

2. CONTAINER - 100s and 1000s (2 mg and 5 mg)

a. We encourage the inclusion of "USP" in the established name.

b. We encourage you to differentiate your different tablet strengths by the use of different colors, boxing, or some other means.

3. INSERT

a. GENERAL COMMENT

Please be consistent throughout the text of the insert as to whether or not the "t" in "trihexyphenidyl" is capitalized.

b. TITLE

Revise the established name to read "Trihexyphenidyl Hydrochloride Tablets, USP". Note: We encourage the inclusion of "USP".

c. DESCRIPTION

i. Revise this section to read:

Trihexyphenidyl HCl is a synthetic antispasmodic. Each tablet, for oral administration, contains 2 mg or 5 mg trihexyphenidyl HCl and the following inactive ingredients: Dibasic ...

Trihexyphenidyl HCl is a white or slightly off white, crystalline powder, having not more than a very faint odor.

Trihexyphenidyl HCl is the substituted piperidine salt, [insert the second chemical name found in the USP 23 monograph]. Its molecular formula is $C_{20}H_{31}NO \cdot HCl$. The structural formula is:

[insert structural formula as it appears in the USP 23 monograph]

d. ACTIONS

i. Revise this section heading to read "CLINICAL PHARMACOLOGY".

ii. Revise the first sentence to read:

Trihexyphenidyl HCl exerts a direct ...

e. INDICATIONS

i. Revise this section heading to read "INDICATIONS AND USAGE".

ii. Revise the first sentence to read:

Trihexyphenidyl HCl tablets are indicated ...

f. DOSAGE AND ADMINISTRATION

Trihexyphenidyl HCl in Idiopathic Parkinsonism, third sentence - ... found to be the optimal ...

g. HOW SUPPLIED

i. We encourage the inclusion of the "CAUTION: Federal Law ..." statement.

ii. Include the "Dispense in ..." statement that appears on your container labels.

h. Per 21 CFR 201.56(e), place the revision date prominently immediately following the last section of the insert.

Please revise your labels and labeling, as instructed above, and submit final print.

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

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 the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours.

12/4/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-184

Circa Pharmaceuticals, Inc.
Attention: Joyce Anne DelGaudio
33 Ralph Street
P.O. Box 30
Copiague, NY 11726-0030

JUN 25 1996

Dear Madam:

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

This is a correction to our letter dated June 13, 1996.

Reference is also made to our "Refuse to File" letter dated May 13, 1996, and your amendment dated June 5, 1996.

NAME OF DRUG: Trihexyphenidyl Hydrochloride Tablets, 2 mg and 5 mg

DATE OF APPLICATION: March 26, 1996

DATE OF RECEIPT: March 27, 1996

DATE ACCEPTABLE FOR FILING: June 6, 1996

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

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

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 594-1300

Sincerely yours,

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

ANDA 40-184
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett
Endorsement: HFD-615/PRickman, Chief,
HFD-615/SMiddledton,CST
HFD-625/BArnwine, Sup. Cl
x:\new\firmsam\circa\ltrs
F/T bcw 6-24-96
ANDA Acknowledgement Letter!

CIRCA PHARMACEUTICALS, INC.
33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

6/11/96

June 5, 1996

Labeling review completed
Dlevine 7-31-96

Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773



11/AC

**RE: ANDA 40-184; TRIHEXYPHENIDYL HCl TABLETS, 2 MG & 5 MG**
**Response to Refuse-to-File Letter**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application, submitted March 26, 1996 pursuant to 21 CFR part 314, subpart C and Section 505(j) of the Federal Food, Drug and Cosmetic Act, for the above mentioned drug product.

Reference is also made to your letter dated May 13, 1996 (copy enclosed), in which the Office of Generic Drugs refused to file the above mentioned application, and our subsequent telephone conversation with Saundra Middleton, Consumer Safety Technician, Office of Generic Drugs, dated May 20, 1996.

The letter indicated that the Office of Generic Drugs was refusing to file our application under 21 CFR §314.101(d)(3), due to the failure of Circa to provide English translations for documents pertaining to the active ingredient. Our telephone conversation with Ms. Middleton confirmed that the specific documents to which this letter pertained, for the active bulk drug substance, appearing in Section VIII, Raw Material Controls, pages 0127B through 0127J.

In this regard, we have enclosed a revised copy of these particle size results, containing an appropriate English translation for all words that are not of the English language. This translation was provided by the manufacturer of the active bulk drug substance . Please note that the translation for was provided by Circa. We have enclosed a copy of page 1525 of The Merck Index, (Eleventh Edition, Merck & Co., Inc., Rahway N.J., U.S.A.; 1989) in support of this translation.

-Continued-

We believe that the information included in this response adequately responds to your letter dated May, 13, 1996. Please do not hesitate to contact us should you have any questions regarding the submitted information.

FIELD COPY CERTIFICATION

Pursuant to 21 CFR 314.96(b), we certify that a true field copy of this amendment has been sent by overnight courier to:

Mr. Edward T. Warner, District Director
Food and Drug Administration (NYK-DO)
850 Third Avenue
Brooklyn, New York 11232-1593

Sincerely,
CIRCA PHARMACEUTICALS, INC.

Joyce Anne DelGaudio
Director, Regulatory Affairs

ANDA 40-184

Circa Pharmaceuticals, Inc.
Attention: Joyce Anne DelGaudio
33 Ralph Ave.
P.O. BOX 30
Copiague NY 11726-0030

MAY 13 1996

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated March 26, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Trihexyphenidyl Hydrochloride Tablets USP, 2 mg and 5 mg.

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 file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> You have failed to provide English translations of all documents not in English. Examples include, but are not limited to your active ingredient. Please review your application and provide translations of all pages not in English [314.50(g)(2)].

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Saundra T. Middleton
Consumer Safety Technician
(301) 594-2290

Sincerely yours,

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

ANDA 40-184
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett
Endorsements: HFD-615/PRickman, Chief DEP date
HFD-615/SMiddleton, C date 5/13/96
HFD-625/BArnwine/Cehm Branc date
WP File x:\new\firmsam\Circa\ltrs&rev\40184rtf.f
F/T by hrw 5-2-96
ANDA Refuse to File Letter!

CIRCA PHARMACEUTICALS, INC.
33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

March 26, 1996

Charles Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773



**RE: TRIHEXYPHENIDYL HCl TABLETS, 2 MG & 5 MG**

Dear Dr. Ganley:

Pursuant to 21 CFR part 314, subpart C and Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting an Abbreviated New Drug Application for trihexyphenidyl HCl tablets, 2 mg & 5 mg.

This submission contains an archival copy (3 volumes in blue jackets) and review copies (3 volumes in red jackets/chemistry, manufacturing and controls technical review section and 1 volume in orange jacket/pharmacokinetics technical review section). These sections comply with the regulations set forth in 21 CFR §314.94(d)(2).

The therapeutic equivalence code for trihexyphenidyl HCl Tablets is AA, according to the Approved Drug Products With Therapeutic Equivalence Evaluations, 15th edition. As a conventional dosage form product "not presenting either actual or potential bioequivalence problems or quality on standards issues", we have included *in vitro* dissolution profiles that compare our test drug product with the listed reference drug product Artane® in Section VI of this ANDA. A request for a waiver of the requirement to conduct bioequivalence studies is also included in Section VI. The waiver is based on the comparative dissolution data of the 2 mg and 5 mg test products to the 2 mg and 5 mg reference drug products.

In July of 1995, Circa Pharmaceuticals, Inc. merged with Watson Laboratories, Inc. of Corona California. One of the outcomes of this merger is the decision that all prescription drug products manufactured at either plant will be labeled as "Manufactured By" Watson Laboratories, Inc.. Therefore, the "Manufactured By" designation of our draft container labels and inserts reflect "Watson Laboratories Inc., Copiague, NY 11726, as does the labeler code of 52544. A revised Form 2656e, Establishment Registration, adding the "Other Firm Name" of Watson Laboratories, Inc. to our Copiague NY address, has been submitted to the Drug Listing Branch

continued...

Following this cover letter, please find the Certification required by the Generic Drug Enforcement Act of 1992, and the Office of Generic Drugs letter dated January 15, 1993. The required patent certification information to show that the drug product provided in this application is the same as the listed drug and a completed Form FDA 356h are also included.

Pursuant to 21 CFR 314.94(d)(5), we certify that a true copy of the chemistry, manufacturing and controls section of this Abbreviated New Drug Application has been sent by overnight courier to:

Mr. Edward T. Warner, District Director
Food and Drug Administration (NYK-DO)
850 Third Avenue
Brooklyn, New York 11232-1593

If you have any questions concerning this ANDA, please contact Joyce Anne DelGaudio at (516) 842-8383.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provision of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

We look forward to your prompt review of the submitted information.

Sincerely,

Joyce Anne DelGaudio

Joyce Anne DelGaudio
Director, Regulatory Affairs

RECORD OF TELEPHONE CONVERSATION

I called Joyce DelGaudio to explain that OGD sent an acknowledgement letter with the wrong date for acceptable filing. Initially Circa received a refuse to file letter dated May 13, 1996. The firm responded with an amendment dated June 5, and received by OGD stamp date, June 6, 1996.

OGD incorrectly sent an acknowledgment letter dated June 13, 1996 with OGD receipt date as of March 27, 1996. I called to tell her that the wrong letter was sent and we would send a new corrected letter with the appropriate receipt date of June 6, 1996.

Joyce said she was surprised when she received the June 13th letter with the old received date. She was a little upset with my phone call but accepted my explanation.

**DATE**
June 21,1996

**APPLICATION NUMBER**
40-184

**IND NUMBER**

**TELECON**

**INITIATED BY** _ **APPLICANT/ SPONSOR**
X **FDA**

**MADE** X **BY TELE.**
_ **IN PERSON**

**PRODUCT NAME**
Trihexphenidyl Hydrochloride Tablets 2 mg and 5 mg

**FIRM NAME**
Circa

**NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD**
Joyce DelGaudio Regulatory Affairs

**TELEPHONE NUMBER**
516-842-8383

**SIGNATURE**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 40184

## ADMINISTRATIVE DOCUMENTS

# DIVISION REVIEW SUMMARY

**ANDA 40-184** **DRUG PRODUCT:** Trihexphenidyl Hydrochloride

**FIRM:** Circa Pharmaceuticals, Inc.

**DOSAGE FORM:** Tablets (Oral) **STRENGTH(S):** 2 mg and 5 mg

**CGMP STATEMENT/EIR UPDATE STATUS:** Pending -
An **ESTABLISHMENT EVALUATION REQUEST** has been issued, dated 8/7/97, to the Division of Compliance to evaluate the CGMP status

**BIO INFORMATION:** Satisfactory -
**Satisfactory letter issued 9/19/96,** see review of dissolution data and waiver request conducted by Moheb H. Makary, concurred by Keith Chan, dated 9/13/96.

**VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):**
**Satisfactory -**
**Drug substance and drug product - Methods validation is not required because Trihexphenidxyl Hydrochloride and Trihexphenidxyl Hydrochloride tablets are compendia items.**

**STABILITY:** Satisfactory -
Accelerated (40°C/75% RH)) stability data are provided for lot nos. RD1126 and RD1137 tested at 0, 4, 8 and 12 weeks in the final marketed container/closure systems (75cc, 250cc and 400cc HDPE bottles). See container/Closure Section for details. The data are adequate and within the specified limits. The container/ closure systems used in the stability studies are the same as those indicated in the container/closure section. **An expiration dating period of 24 month has been granted.**

**LABELING:** Satisfactory -
See review of professional labeling conducted by Angela Payne, concurred by John Grace, dated 5/14/97.

**STERILIZATION VALIDATION:** N/A

**SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?)** Satisfactory - Executed Batch Records with equipment specified, including packaging records, batch reconciliation and label reconciliation are provided for lots number RD1126 (2 mg) and RD1137 (5 mg).

Lot number RD1126 (2 mg tab.)has a theoretical yield of tablets, actual yield of tablets.

which includes a

Lot no. RD1137 (5 mg tab.) has a theoretical yield of tablets, actual yield of tablets.

which includes a

**found adequate, dated 4/10/97.**

**SIZE OF STABILITY BATCHES - Satisfactory -**
Lot number RD1126 (2 mg tab.)has a theoretical yield of tablets, actual yield of tablets . **A five percent overage of the active bulk substance has been added to the master formula.** Final blend reconciliation is tablet reconciliation of which includes a accountable waste. The formula appears accurate and the instructions are clear, logical and comprehensive. Batch Reconciliation indicates the entire batch was compressed. The lot was manufactured on production equipment under actual production conditions.

Lot no. RD1137 (5 mg tab.) has a theoretical yield of tablets, actual yield of tablets **A five percent overage of the active bulk substance has been added to the master formula.** Final blend reconciliation is nd tablet reconciliation of which includes a accountable waste. The formula appears accurate and the instructions are clear, logical and comprehensive. Batch Reconciliation indicates the entire batch was compressed. The lot was manufactured on production equipment under actual production conditions.

**PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?**

The intended maximum production batch sizes are and tablets, 2 mg and 5 mg tablets respectively, with equipment specified. Both of the batch size increases are in compliance with OGD Policy and Procedure Guide 22-90 and the ten-fold scale-up.

**RECOMMENDATION:**

**APPROVE**

cc: ANDA #40-184
~~Division File~~
~~Field Copy~~

Endorsements:

8/29/97

HFD-645/RBrown/8/15/97
HFD-645/BArnwine/8/28/97

9/9/97

F/T by at/8/28/97
X:/NEW/FIRMSAM/CIRCA/LTRS&REV/40-184.APF

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

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Date of Review: July 31, 1996

ANDA Number: **40-184** Review Cycle: **1** (draft)

Dates of Submission: March 26, 1996 (Original Submission - RTF)
June 5, 1996 (AC)

Applicant's Name [as seen on 356(h)]: **Circa Pharmaceuticals, Inc.**

Manufacturer's Name (If different than applicant):
**Watson Pharmaceuticals, Inc.**

Proprietary Name: None

Established Name:
**Trihexyphenidyl Hydrochloride Tablets USP, 2 mg and 5 mg**

Reviewer: David Konigstein

---

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

1. GENERAL COMMENT

   Please be consistent throughout your labels and labeling regarding "Inc." in the manufacturer's name.

2. CONTAINER - 100s and 1000s (2 mg and 5 mg)

   a. We encourage the inclusion of "USP" in the established name.

   b. We encourage you to differentiate your different tablet strengths by the use of different colors, boxing, or some other means.

3. INSERT

   a. GENERAL COMMENT

      Please be consistent throughout the text of the insert as to whether or not the "t" in "trihexyphenidyl" is capitalized.

   b. TITLE

      Revise the established name to read

"Trihexyphenidyl Hydrochloride Tablets, USP".
Note: We encourage the inclusion of "USP".

c. DESCRIPTION

i. Revise this section to read:

Trihexyphenidyl HCl is a synthetic antispasmodic. Each tablet, for oral administration, contains 2 mg or 5 mg trihexyphenidyl HCl and the following inactive ingredients: Dibasic ...

Trihexyphenidyl HCl is a white or slightly off white, crystalline powder, having not more than a very faint odor.

Trihexyphenidyl HCl is the substituted piperidine salt, [insert the second chemical name found in the USP 23 monograph]. Its molecular formula is $C_{20}H_{31}NO \bullet HCl$. The structural formula is:

[insert structural formula as it appears in the USP 23 monograph]

d. ACTIONS

i. Revise this section heading to read "CLINICAL PHARMACOLOGY".

ii. Revise the first sentence to read:

Trihexyphenidyl HCl exerts a direct ...

e. INDICATIONS

i. Revise this section heading to read "INDICATIONS AND USAGE".

ii. Revise the first sentence to read:

Trihexyphenidyl HCl tablets are indicated ...

f. DOSAGE AND ADMINISTRATION

Trihexyphenidyl HCl in Idiopathic Parkinsonism, third sentence - ... found to be the optimal ...

g. HOW SUPPLIED

i. We encourage the inclusion of the "CAUTION: Federal Law"... statement.

ii. Include the "Dispense in ..." statement that appears on your container labels.

h. Per 21 CFR 201.56(e), place the revision date prominently immediately following the last section of the insert.

Please revise your labels and labeling, as instructed above, and submit final print.

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

---

# REVIEW OF PROFESSIONAL LABELING CHECKLIST

| Applicant's Established Name | Yes | No | N.A. |
|---|---|---|---|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. | X | | |
| Is this name different than that used in the Orange Book? | | X | |
| If not USP, has the product name been proposed in the PF? | | | X |
| **Error Prevention Analysis** | | | |
| *PROPRIETARY NAME* - None | | | |
| *PACKAGING* -See applicant's packaging configuration in FTR | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | | X |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | | X | |

| | | | |
|---|---|---|---|
| Are there any other safety concerns? | | X | |
| *LABELING* | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? **Comment made.** | X | | |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | X | |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| **Scoring:** Describe scoring configuration of RLD and applicant (p. #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | | X | |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | X | |
| **Inactive Ingredients:** (FTR: List p. # in application where inactives are listed) | | | |
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray? | | | X |
| Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION? | | | X |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | | X |
| **USP Issues:** (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |

| | | | |
|---|---|---|---|
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | | X | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.<br>**RLD INSERT FROM 1987. DIDN'T HAVE. COMMENT MADE TO INCLUDE.** | X | | |
| **Bioequivalence Issues: Pending** | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| **Patent/Exclusivity Issues:** FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | X | |

---

## FOR THE RECORD:

1. MODEL LABELING - NDA 6-773/SLR-022: Artane®; Lederle Laboratories; Revised 4/87; Approved 7-24-87.

2. NOTEWORTHY - Circa was acquired by Watson Labs. Circa explains in their cover letter that their product will have a Mfg By statement that has Watson as the mfg with the address of Circa. This is ok under 201.1(g) and they indicate the proper documentation has been filed with FDA's Drug Listing Branch.

3. INACTIVE INGREDIENTS - See pp. 113-14. The listing of inactives is satisfactory.

4. PATENTS/EXCLUSIVITIES - N/A

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON - Both RLD and ANDA have "Store at CRT 15°-30°C (59°-86°F)". USP has no recommendation.

6. DISPENSING STATEMENTS COMPARISON - USP, ANDA and RLD - Tight container.

7. BIOEQUIVALENCE - Pending. Waiver requested for in-vivo studies. Dissolution and content uniformity data are submitted.

8. PACKAGING CONFIGURATIONS -
   Per Facts and Comparisons (this page has a revision date of 5/90), the RLD is available as 2 mg tablets in 100s, 1000s and Unit-Dose 100s and the 5 mg in 100s and

Unit-Dose 100s. They also market a 2 mg/5 mL elixir in 480 mL and a 5 mg sustained release capsule.

The ANDA proposes bottles of 100s and 1000s for each strength. All with non-CRC closure.

9. The tablet debossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. Apparently, the initial work was done with tablets dressed for Circa, then when Watson entered the picture, the tablet markings were changed. Old Circa markings appear on pp. 800 and 806. The current markings appear on finished product specification documents (pp. 590 and 598).

10. SCORING - Both ANDA and RLD are scored. RLD confirmed by pictures in 1995 PDR.

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David Konigstein 8-5-96
Primary Reviewer Date

Adolph Vezza 8-5-96
Acting Team Leader, Labeling Review Branch Date

cc: ANDA 40-184
Dup
Division File

F/T by DK 8-5-96
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REVIEW