CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40277

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 40-277 **SPONSOR:** Taylor Pharmaceuticals

DRUG & DOSAGE FORM: Proparacaine Hydrochloride Ophthalmic Solution, USP

STRENGTH: 0.5%

TYPE OF STUDY: **SD** **SDF** **MULT** **OTHER** Waiver Request

STUDY SITE: NA **CLINICAL:** NA **ANALYTICAL:** NA

STUDY SUMMARY:

The listed reference product is 0.5% Ophthaine® Ophthalmic Solution manufactured by Apothecon. The product is coded AT in the Therapeutic Equivalence List suggesting no known or suspected bioequivalence problems. The reference and test products are intended for identical indications. The test product contains the same inactive ingredients in identical strength to the reference product (within ±5%) except for omission of the antimicrobial preservative chlorobutanol from the test product.

The Division of Bioequivalence agrees that the information submitted by Taylor Pharmaceuticals demonstrates that its Proparacaine Hydrochloride Ophthalmic Solution, 0.5%, falls under CFR 320.24(b)(6) of the Bioavailability/Bioequivalence Regulations. The waiver of *in-vivo* bioequivalence study requirements for the 0.5% proparacaine ophthalmic solution of the test product is granted. The 0.5% proparacaine ophthalmic solution of the test product is deemed bioequivalent to 0.5% Ophthaine® Ophthalmic Solution manufactured by Apothecon

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DISSOLUTION : Not applicable

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I

INITIAL: S **DATE:** 1/7/98

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I

INITIAL: S **DATE:** 1/7/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: S **DATE:** 1/12/98

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: _____ **DATE:** _____

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-277 APPLICANT: Taylor Pharmaceuticals

DRUG PRODUCT: Proparacaine Hydrochloride, Ophthalmic Solution, USP, 0.5%

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

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

Sincerely yours,

/S/

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

Proparacaine Hydrochloride
Ophthalmic Solution, USP, 0.5%
ANDA # 40-277
Reviewer: J. Chaney

Taylor Pharmaceuticals
Decatur, IL
Submission Date:
September 11, 1997

Review of a Waiver Request

Proparacaine hydrochloride is a water-soluble local anesthetic. It is applied topically to the eye to anesthetize the conjunctiva and cornea and provide sufficient analgesia for superficial procedures.

Taylor Pharmaceuticals (known as Akorn Manufacturing, Inc. prior to August 21, 1996) has requested a waiver of bioequivalence study requirements for the test product under 21 CFR 320.22 (b)(1)(i)&(ii) of the Bioavailability/Bioequivalence Regulations. The formulation of the test product in comparison with the reference listed product, Ophthaine®, currently manufactured by Apothecon, Inc. (a Bristol-Myers Squibb company) which was approved on 07/01/53 under NDA #08883 is shown in the following table:

(COMPOSITION NOT TO BE RELEASED THROUGH FOI)

Comparative Formulations of Taylor's Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5% and the Reference Ophthaine®, Manufactured by Apothecon, Inc.

Ingredient	Test Product (Each mL)	Reference Product* (Each mL)	T/R
Proparacaine HCl, USP (*)	5.25 mg**	5.0 mg	1.05
Benzalkonium chloride, NF	0.10 mg	0.10mg	1.00
Glycerin USP	24.0 mg	24.5 mg	0.98
NaOH NF	pH 3.5-6.0	pH 3.5-6.0	--
HCl NF	pH 3.5-6.0	pH 3.5-6.0	--
Water for injection, USP	qs to 1 mL	qs to 1 mL	--

* As determined by the reviewer from the Drug Product Reference File (DPRF) (COMIS).

** The 5.25mg/ML includes a 5% overage of proparacaine HCl.

The following table shows the comparison of osmolarity and pH between the test and reference Ophthaine® for further confirmation of equivalency:

Physical Property	Test (Lot 21206)	Reference
pH	4.58	5.0
Osmolality (mOsm/kg)	293	312

Comments

1. FDA regulations at 21 CFR 314.94 (a) (9) (iv) state in pertinent part: "..a drug product intended for ophthalmic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug...However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information... demonstrating the differences do not affect the safety of the proposed drug product..."

2. The inactive ingredients are qualitatively identical in the test and reference products except for omission of the antimicrobial preservative chlorobutanol in the test product.

3. The corresponding inactive ingredients in the test and reference products are quantitatively identical except for glycerin for which the difference between test and reference products is two percent.

4. The firm cited 21 CFR 320.22(b)(1)(i)&(ii) of the Bioavailability/Bioequivalence Regulations in its waiver request. - Since the formulations of the test and reference products are not identical in that the test product does not contain the antimicrobial chlorobutanol present in the reference, the waiver should be granted under 21 CFR 320.24(b)(6).

Recommendations

The Division of Bioequivalence agrees that the information submitted by Taylor Pharmaceuticals demonstrates that its proparacaine hydrochloride ophthalmic solution USP, 0.5% falls under the criteria set forth in 21 CFR 320.24 (b)(6) of the Bioavailability/Bioequivalence Regulations. The waiver of the *in-vivo* bioequivalence study requirements for the 0.5% proparacaine ophthalmic solution (test product) is granted. From the bioequivalence point of view the Division of Bioequivalence deems the test ophthalmic product to be bioequivalent to Opthaine® solution manufactured by Bristol Myers Squibb.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 1/7/98

Concur /S/ Date 1/12/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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