CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 40-458

BIOEQUIVALENCE REVIEW(S)

#3

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 40-458 **SPONSOR:** Mikart Inc.

DRUG AND DOSAGE FORM: Carbinoxamine Maleate

STRENGTH: 4 mg/5 mL

TYPES OF STUDIES: Request for biowaiver

CLINICAL STUDY SITE (S): N/A

ANALYTICAL SITE (S): N/A

STUDY SUMMARY: N/A

DISSOLUTION/BIOWAIVER: Biowaiver is acceptable.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic **YES** New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : CHANDRA S. CHAURASIA, Ph. D. BRANCH : I

INITIAL : Chandra S. Chaurasia DATE : 2/12/2002

TEAM LEADER : YIH-CHAIN HUANG, Ph. D. BRANCH : I

INITIAL : Y H H DATE : 2/12/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for INITIAL : N Gabrielsson DATE : 2/14/2002

Carbinoxamine Maleate [redacted]
4 mg/5 mL
ANDA 40-458
Reviewer: Chandra S. Chaurasia
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Mikart Inc.
Atlanta, GA
Submission Date:
Nov 15, 2001

Review of a Waiver Request

BACKGROUND

First Generic: Yes

1. The firm has requested a waiver of *in vivo* bioequivalence study requirements for its drug product, Carbinoxamine Maleate [redacted] 4 mg/5 mL in accordance with CFR 320.22(b)(3).
2. **Reference Listed Drug**: At present no RLD is listed in the Orange Book. Two oral dosage forms of carbinoxamine maleate — Clistin® tablets (NDA 8-915) 4 mg and Clistin® elixir, 4 mg/5 mL (NDA 8-955) approved prior to Jan 1, 1982, manufactured by R.W. Johnson — are listed in the Discontinued Drug Product Section of the Orange Book (Electronic 2002).
3. In response to a citizen's petition dated October 08, 1999 (Docket No. 99P-4848/CP1) submitted by Mikart Inc., the Agency had determined that the drug product carbinoxamine maleate (Clistin, NDA 8-955) elixir, 4mg/ 5 mL was not withdrawn from marketing for safety or efficacy reasons (Federal Register Vol. 65, No. 69, p. 18998).
4. The following information on carbinoxamine was obtained from Micromedex Integrated Index:

   Carbinoxamine maleate is an ethanolamine antihistamine. It is effective for the symptomatic relief of seasonal and perennial allergic rhinitis and vasomotor rhinitis.

   Dosing Information: The normal oral adult dosage is 4 to 8 milligrams three times a day. The normal oral pediatric dosages are 2 mg three or four times a day (ages 1 to 3), 2 to 4 mg three or four times a day (ages 3 to 6), and 4 to 6 mg three or four times a day (ages over 6).

FORMULATION (Not to be released under FOI)

Components and composition of the test products are as follows:

Ingredient	Test Product Quantity per 5 mL	% Composition
Carbinoxamine Maleate, USP	4 mg	0.08
Sorbitol Solution, USP	[redacted]	[redacted]
Glycerin, USP	[redacted]	[redacted]
Propylene Glycol, USP	[redacted]	[redacted]
Sodium Citrate Hydrous, USP	[redacted]	[redacted]
Citric Acid Anhydrous	[redacted]	[redacted]
Methylparaben	[redacted]	[redacted]
Propylparaben	[redacted]	[redacted]
Artificial Bubble Gum Flavor [redacted]	[redacted]	[redacted]
Purified Water, USP	[redacted]	[redacted]

**Reported as volume to volume (%v/v), all others reported as weight to volume (%w/v)*

COMMENTS

1. The test drug product contains the same active ingredient in the same concentration as the previously approved reference listed product Clistin elixir, 4mg/ 5 mL, and is intended solely for administration by oral route. As mentioned above, the Agency had determined that the drug product Clistin elixir, 4mg/ 5 mL was not withdrawn from marketing for safety or efficacy reasons.

2. All inactive ingredients utilized in the formulation are within the listed levels in the Inactive Ingredient Guide (1996) for oral product except artificial bubble gum flavor. The inactive ingredient, bubble gum flavor is not listed in the IIG. The breakdown of this flavoring agent (as provided by the firm) indicates propylene glycol as the main constituent [redacted]. In addition, the amount of each constituent in the bubble gum flavor is less than [redacted] of the total formulation of the test drug product.

   The concentration of sorbitol in the Test product is [redacted] v/v. It is noted that this inactive ingredient has been used in as high as [redacted] (Hycomine, Endo), [redacted] (Thioridazine HCl, Alpharma) and [redacted] (Symmetrel Syrup, Endo Pharms) concentrations.

   Reviewer's Note: *The COMIS Data Base search indicates [redacted] mL as the only inactive ingredient in the NDA Clistin Elixir 4 mg/5 mL* ***(Not to be release under FOI).***

3. The waiver of *in vivo* bioequivalence study requirements may be granted based on 21 CFR 320.22(b)(3) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Mikart Inc. demonstrates that its Carbinoxamine Maleate [redacted] 4mg/5 mL falls under 21 CFR 320.22(b)(3) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for Carbinoxamine Maleate [redacted] 4mg/5 mL of the test product is granted.

Chandra S. Chaurasia

Chandra S. Chaurasia, Ph. D.
Division of Bioequivalence
Review Branch I

Date: 2/12/2002

RD INITIALLED YHUANG
FT INITIALLED YHUANG Date: 2/12/2002

Concur Date: 2/14/2002

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

ANDA 40-458 Carbinoxamine Maleate ~~4~~ 4 mg/5 mL Mikart Inc.
CC: DIVISION FILE, HFD-652/Bio Secretary-Bio Drug File, HFD-650/C.Chaurasia
V:\firmsam\Mikart\ltrs&rev\40458w1101

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #40-458
ANDA DUPLICATE
DIVISION FILE
HFD-650/Bio Secretary-Bio Drug File
HFD-652/C. Chaurasia

Endorsements: (Draft and Final with Dates)

HFD-652/CS Chaurasia CSChaurasia 2/12/2002
HFD-652/YC Huang YCH 2/12/2002
HFD-617/K Scardina KS 2/15/02
HFD-650/Dale Conner for DAC 2/14/2002

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Printed In Final On 02/12/02

BIOEQUIVALENCY – ACCEPTABLE **Submission Date: Nov 15, 2001**

WAIVER (WAI) ok

Strength: 4mg/5mL
Outcome: AC

Outcome Decisions: Acceptable
AC - Acceptable

WINBIO COMMENTS: The waiver is granted

APPEARS THIS WAY
ON ORIGINAL

40458 Please file in latest open BIO volume 1.1

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : November 28, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 28-NOV-2001

SUBJECT: Examination of the request for waiver submitted with an ANDA for Carbinoxamine Maleate ——, Oral 4 mg/5 mL to determine if the application is substantially complete for filing.

4587

Mikart Inc. submitted ANDA 40-548 for Carbinoxamine Maleate ——, Oral 4 mg/5 mL. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for waiver submitted by Mikart on November 15, 2001 for its Carbinoxamine Maleate product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

1.1

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

Concur;
Barbara M. Saint
Team Leader
1/14/02

_____ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

_____ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence — Date: 1/15/02

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 40-458 DRUG NAME CARBINOXAMINE MALEATE FIRM MIKART, INC

DOSAGE FORM(s) ORAL (4mg/5mL)

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol		✓			N/A
Assay Methodology		✓			N/A
Procedure SOP		✓			N/A
Methods Validation		✓			N/A
Study Results Ln/Lin		✓			N/A
Adverse Events		✓			N/A
IRB Approval		✓			N/A
Dissolution Data		✓			N/A
Pre-screening of patients		✓			N/A
Chromatograms		✓			N/A
Consent forms		✓			N/A
Composition	✓				LISTED IN IIG EXCEPT FLAVOR
Summary of study		✓			N/A
Individual Data & Graphs , Linear & Ln		✓			N/A
PK/PD data disk		✓			N/A
Randomization Schedule		✓			N/A
Protocol Deviations		✓			N/A

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site		✓			N/A
Analytical site		✓			N/A
Study investigators		✓			N/A
Medical Records		✓			N/A
Clinical Raw Data		✓			N/A
Test Article Inventory		✓			N/A
BIO Batch Size		✓			N/A
Assay of active content drug		✓			N/A
Content uniformity		✓			N/A
Date of manufacture		✓			N/A
Exp. Date RLD		✓			N/A
Biostudy lot numbers		✓			N/A
Statistics		✓			N/A
Summary results provided by the firm indicate studies pass BE criteria		✓			N/A
Waiver requests for other strengths / supporting data	✓				RLD (CLISTIN®) UNDER BIOWAIVER STATUS. MIKART, REQUESTING BIOWAIVER UNDER 21 CFR 320.22.

Additional comments:

RLD (CILISTIN®) WITHDRAWN FROM SALES FOR REASONS NOT RELATED TO SAFETY/EFFECTIVENESS AND IS CURRENTLY LISTED IN THE DISCONTINUED DRUG PRODUCT LIST OF THE ORANGE BOOK.

INGREDIENTS OF GENERIC PRODUCT LISTED IN THE IIG EXCEPT ARTIFICIAL BUBBLE GUM FLAVOR(——— PROPYLENE GLYCOL). FIRM SENT BREAKDOWN OF THE FLAVOR. THEREFORE, COMPOSITION IS ACCEPTABLE

The RS was not withdrawn for reasons of safety or effectiveness.

[Docket No. 99P-4848]

See FR Vol 65 No 69 Monday Apr 10, 2000 page 18998

Recommendation: (COMPLETE) / INCOMPLETE

Reviewed by

PATRICK NWAKAMA Date 1/14/2002

Revised 6/7/2000

concur:

Barbara Schwartz 1/14/02

BIOEQUIVALENCY COMMENTS

ANDA: #40-458 APPLICANT: Mikart, Inc.

DRUG PRODUCT: Carbinoxamine Maleate ——. 4mg/5 mL

The Division of Bioequivalence has completed its review of your application 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,

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