

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: NDA 20-726/S-006

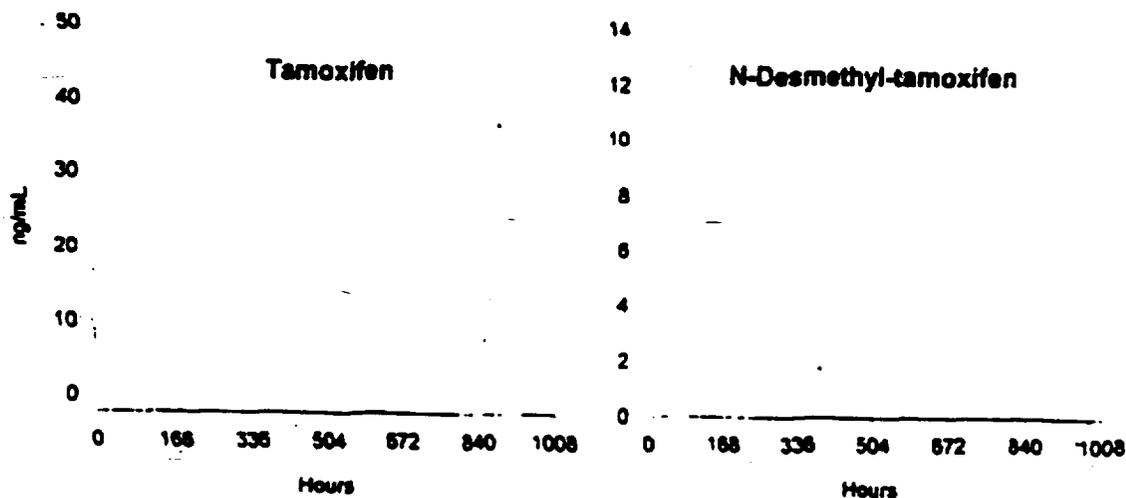
**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

investigation was requested and has been completed. Please see the Division of Scientific Investigation's (DSI) review of an EIR in Appendix III.

This review is completed by Question Based Review (QBR) approach focusing on the bioequivalence between the generic formulation, Tamofen and the US approved formulation, Nolvadex.

1. Has the bioequivalence between the generic formulation and the innovator formulation been established?

The applicant submitted the results of a bioequivalence study (Study P102). This is an open-label, randomized, single oral dose (20 mg), two-period, two-way crossover study, with washout period 13-week. The study conducted in 36 postmenopausal women. The pharmacokinetics showed that treatments with Tamofen and Nolvadex led to similar plasma concentration profiles for both tamoxifen and the major metabolite, N-desmethyltamoxifen as shown in the following figure obtained from the submission.



The analysis of the pharmacokinetic parameters, C_{max} and AUC, showed that the 90% confidence intervals for the ratio of test product to reference product were within the 80 to 125% bioequivalence range for both tamoxifen and N-desmethyltamoxifen. The results are summarized in the following table.

Table. Summary of the results of the bioequivalence study

Parameters	Compound	Ratio (B/A)	90% confidence interval	
			Lower	Upper
AUC _{inf}	Tamoxifen	95.5	90.3	101.1
C _{max}	Tamoxifen	98.3	92.8	105.1
AUC _{inf}	N-desmethyl-tamoxifen	95.6	88.1	103.8
C _{max}	N-desmethyl-tamoxifen	99.3	93.6	105.3

Therefore, the generic form of tamoxifen, Tamofen is considered to be bioequivalent to Nolvadex.

After the on-site investigation, Division of Scientific Investigation (DSI) found the data from subject 125, 127, 130, and 131 in period 1 for tamoxifen and/or desmethyltamoxifen unacceptable and recommended excluding these data for bioequivalence analysis. The reviewer reanalyzed the data based on this recommendation, and concludes that exclusion of the data from 4 subjects does not alter the outcome of the study. The reanalysis results are summarized in the following table.

Parameters	Compound	Ratio (B/A)	90% confidence interval	
			Lower	Upper
AUC _{inf}	Tamoxifen	96.4	90.9	102.4
C _{max}	Tamoxifen	97.9	92.0	104.2
AUC _{inf}	N-desmethyl-tamoxifen	95.8	87.5	104.9
C _{max}	N-desmethyl-tamoxifen	96.5	90.3	103.0

2. Is the assay for the bioequivalence study acceptable?

Tamoxifen and its major metabolite N-desmethyltamoxifen in plasma were analyzed by a _____ with _____ after _____ with _____

The assay validation results from the analytical report are presented in the following table.

Species	Tamoxifen	N-desmethyltamoxifen
Method	-----	-----
Quantifiable Range	-----	-----
Precision (%CV)	-----	-----
Accuracy (%bias)	-----	-----

Based on the current standard, the assay is adequate. However, on-site investigation found that tamoxifen and/or desmethyltamoxifen concentration data for subject 125, 127, 130, and 131 in period 1 may not be accurate due to column degradation or unacceptable practice

See Appendix III DSI Memorandum for details.

II. GENERAL COMMENTS

1. Tamofen is considered to be bioequivalent to the US innovator formulation Nolvadex based on the study results submitted.

III. RECOMMENDATIONS

Tamofen is considered to be bioequivalent to the US approved formulation Nolvadex. Therefore, the use of this generic form of tamoxifen as an active comparator in the pivotal

clinical trials should be acceptable.

Based on the recommendation from DSI, the reviewer reanalyzed the data of bioequivalence study without subjects 125, 127, 130, and 131 in period 1 for tamoxifen analysis and without subjects 127, 130, and 131 in period 1 for desmethyltamoxifen analysis. It is found that exclusion of the above data does not have significant impact on the bioequivalence between test and reference tamoxifen products.

151

John Duan, Ph.D.

12/18/00

Date

Reviewer
Division of Pharmaceutical Evaluation I

151

Atiqur Rahman, Ph.D.

12/18/00

Date

Team Leader
Division of Pharmaceutical Evaluation I

CC: NDA 20-726 original
HFD-150 Division File
HFD-150 AStaten
HFD-150 MCohen
HFD-150 JJohnson
HFD-860 MMehta, ARahman, JDuan
HFD-48 Vishwanathan, MYau
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TABLE OF CONTENTS

I. SYNOPSIS..... 1

II. GENERAL COMMENTS 3

III. RECOMMENDATIONS..... 3

TABLE OF CONTENTS 5

APPENDIX I. ~~DRAFT~~ LABELING 6

APPENDIX II. INDIVIDUAL STUDY SYNOPSIS 26

 1. *BIOEQUIVALENCE STUDY, PROTOCOL 102* VOLUME: P22.1 - P22.4 26

APPENDIX III. DIVISION OF SCIENTIFIC INVESTIGATIONS MEMORANDUM.....28

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P.P. 6-24

19 pages redacted from this section of
the approval package consisted of draft labeling

References	Vol.	Page
1. Clinical Trial Report for P025: Double blind, double dummy, randomized, multicenter, 2-arm, Phase III trial comparing letrozole 2.5 mg versus tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer. Clinical Trial Report, Novartis Pharma AG, Basle, Switzerland. July 5, 2000.	6	1
2. Clinical Trial Report for P025	6	50
3. Clinical Trial Report for P024: Preoperative hormone therapy for postmenopausal women with ER and/or PgR positive breast cancer: A double blind randomized parallel group phase IIb /III trial, comparing the efficacy of 4 months preoperative letrozole (2.5 mg daily) with preoperative tamoxifen (20 mg daily).	30	1
4. Clinical Trial Report for P024	30	30
5. Integrated Summary of Efficacy for Femara	35	1
6. Clinical Trial Report for P025	6	61
7. Clinical Trial Report for P024	30	36
8. Integrated Summary of Safety for Femara	36	50
9. Clinical Trial Report for AR/ET1/1A: An open, non-comparative, single center phase I trial examining the effect of once daily doses of 2.5 mg and 10 mg CGS 20267 on the intratumoral uptake and synthesis of estrogens in postmenopausal patients with previously untreated locally advanced breast cancer. Novartis Pharma AG, Switzerland, 27 Oct 99.	Please refer to Femara IND [redacted] submission dated 6/29/99 (Serial No. 236) for complete report	

APPENDIX II. INDIVIDUAL STUDY SYNOPSIS

1. *Bioequivalence study, Protocol 102* VOLUME: P22.1 - P22.4

Study title: A Single-Dose, Randomized, Open-Label, Crossover Study Comparing Generic Tamoxifen Citrate Tablets and Nolvadex® Tablets in Postmenopausal Women

Investigator: Dr S Freestone, Dr L Geertsema, Dr M Turner.

Study period: December 2, 1999 to July 3, 2000.

Study formulations:

- Test product: Generic tamoxifen citrate (Tamofen, Leiras Oy, Finland tablets, containing 20 mg tamoxifen: Batch 17/299/50.
- Reference product: Nolvadex® tamoxifen citrate (AstraZeneca Pharmaceuticals, Delaware, USA) tablets, containing 20 mg tamoxifen: Batch 37578 [NDC 0310-0604].

Objectives:

- To compare the rate and extent of absorption of tamoxifen from generic tamoxifen citrate 20 mg tablets (Tamofen, Leiras Oy), with that of the reference formulation Nolvadex® tamoxifen citrate 20 mg tablets (AstraZeneca), following a single dose in postmenopausal women under fasting conditions.

Subjects: 36 Postmenopausal Women

Study Design:

This was an open-label, single dose (20 mg), randomized, two period, two-way crossover bioequivalence study in postmenopausal women.

Plasma tamoxifen and the major metabolite, N-desmethyltamoxifen, concentrations were monitored to evaluate pharmacokinetics. The criteria for evaluation for safety were physical examination, vital signs, ECG, laboratory test results and reported adverse events.

The pharmacokinetic analyses were descriptive statistics for log-transformed and untransformed C_{max} , AUC_{last} , $AUC_{0-\infty}$, and $t_{1/2}$ as well as untransformed t_{max} . ANOVA (analysis of variance) was used to assess the pharmacokinetic comparisons among formulations for C_{max} , $AUC_{0-\infty}$ and AUC_{last} . The effects due to sequence, subject within sequence, period and treatment were evaluated. Bioequivalence was concluded if the 90% confidence intervals of C_{max} and AUC for the ratio of geometric means of test and reference intervals fell within the standard bioequivalence range of 80-125%.

Results:

Assay performance: The assay validation results based on the analytical report are presented in the following table.

Tamoxifen.

Method
Quantifiable Range
Precision (%CV) E
Accuracy (%bias)

Pharmacokinetics:

The pharmacokinetic results of the study showed that treatment with the generic tamoxifen tablet formulation leads to similar plasma concentration profiles for both tamoxifen and desmethyltamoxifen, as seen with those of the US innovator formulation. The statistical analysis of the pharmacokinetic parameters, C_{max} and AUC, showed that the 90% confidence intervals were within the 80 to 125% bioequivalence range for both tamoxifen and desmethyltamoxifen (see Table below).

Table. Summary of the results of the bioequivalence study

Parameters	Compound	Ratio (B/A)	90% confidence interval	
			Lower	Upper
AUC_{inf}	Tamoxifen	95.5	90.3	101.1
C_{max}	Tamoxifen	98.3	92.8	105.1
AUC_{inf}	N-desmethyl-tamoxifen	95.6	88.1	103.8
C_{max}	N-desmethyl-tamoxifen	99.3	93.6	105.3

Therefore, the generic form of tamoxifen, Tamofen is deemed to be bioequivalent to Nolvadex.

Safety

There were no serious adverse events reported during the conduct of this study.

Comments:

1. This study showed the bioequivalence between the generic formulation Tamofen and US approved formulation Nolvadex.

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ON ORIGINAL**