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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-574

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-574	**Relevant IND(s):**	55,962
Submission Type:	Amendment (A2) – Response to 17 October 2003 Approvable Letter		
Submission Date(s):	19 December 2003		
Sponsor Name:	Andrx Laboratories, Inc., Hackensack, NJ		
Brand Name:	FORTAMET™		
Generic Name:	Metformin Hydrochloride Extended Release Tablets		
Indication(s):	Treatment of Type 2 Diabetes Mellitus		
Strength(s):	500-mg and 1000-mg		
Reviewer:	Steven B. Johnson, Pharm.D. / Xiao Xiong "Jim" Wei, M.D., Ph.D.		
Team Leader:	Hae-Young Ahn, Ph.D.		
OCPB Division:	DPE-2 (HFD-870)		
OND Division:	DMEDP (HFD-510)		

Executive Summary

This submission was the response to the approvable letter issued by the Agency on 17 October 2003 for NDA 21-574. The letter stated that the following Clinical Pharmacology and Biopharmaceutics requirements were necessary for the approval of FORTAMET™:

> "... it will be necessary for you to provide sufficient data to demonstrate dosage form equivalence between the 500-mg and 1000-mg tablets."
>
> "In addition, it will be necessary for you to submit revised labeling with the revisions indicated in the enclosed labeling. ... Revise the language under the CLINICAL PHARMACOLOGY section, Pharmacokinetics and Drug Metabolism subsection, Immediate-Release subsection"

In order to satisfy the first requirement, the sponsor conducted a study to evaluate dosage-form equivalence between two FORTAMET™ 500-mg tablets and one FORTAMET™ 1000-mg tablet. Results suggested that when these products are administered under fed conditions, then they are dosage-form equivalent using bioequivalence criteria.

The second requirement was to address labeling issues. The sponsor complied with this request.

In addition to those requirements listed above, and in consultation with Dr. Xiao Xiong "Jim" Wei, the primary CPB reviewer of the original application, the dissolution method and release specifications were inappropriate for this product. The sponsor used a [ ] buffer medium with a pH [ ] This is generally not acceptable to the Agency, especially when the data indicates that dissolution is pH independent for the product – as is the case with FORTAMET™. Therefore, a pH 6.8 phosphate buffer medium was recommended to the sponsor. Also, a recommendation to change the 8-hour and 16-hour release specifications for both strengths of FORTAMET™ was made to better reflect the dissolution characteristics of the product.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics finds the data submitted in NDA 21-574, amendment 2, to be acceptable providing the sponsor agrees to the recommendations described in the **Comments to Sponsor** section of this review.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Comments to Sponsor

1. The proposed dissolution medium, pH[ ].[ ] [ ] buffer is inappropriate for your product given the pH independent dissolution characteristics of FORTAMET™. In addition, the tolerance specifications are too loose for the 8 and 16-hour time points given the data presented to the Agency in both this and the original submission. The interim dissolution method and specifications recommended by the Agency for FORTAMET™ 500-mg and 1000-mg tablets are listed in the following table:

Apparatus		USP Apparatus 1 (basket) [ ]
Medium		0.05M [ ] phosphate buffer, **pH 6.8**
Volume		900 ml
Temperature		37° C
Speed		— RPM
Specification	**500 mg**	2 hr: NMT —, **8 hr:** — **, 16 hr: NLT** —.
	1000 mg	2 hr: NMT — **8 hr:** — **, 16 hr: NLT** —

2. When describing discrete time points, i.e., T_{max}, use range – not standard deviation.

3. Please address labeling changes as directed by the FDA Project Manager.

Steven B. Johnson, Pharm.D.
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

Concur
e-mail
PFS
2/9/04

RD initialed by Hae-Young Ahn, Ph.D., Team Leader:

FT initialed by Hae-Young Ahn, Ph.D., Team Leader:

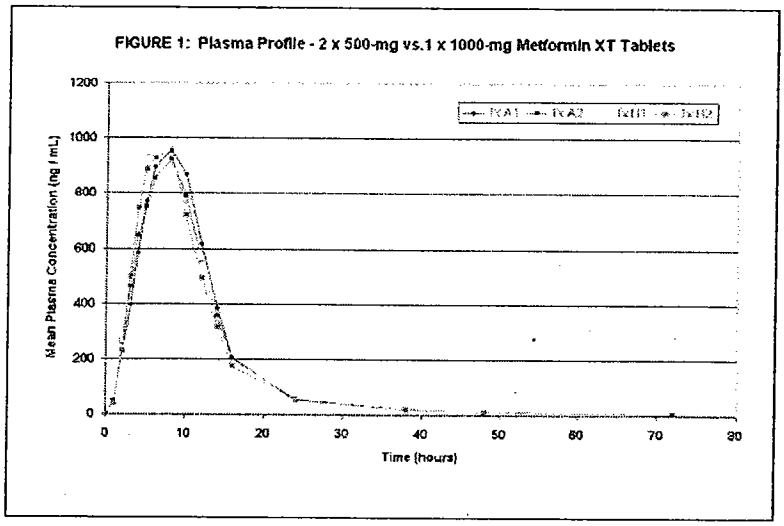
Appears This Way
On Original

Dosage-form Proportionality (Study 155-116)
In order to satisfy the requirement of providing sufficient evidence to demonstrate that the two strengths of FORTAMET™ tablets were dosage-form proportional, the sponsor conducted a single-dose, four-period replicated crossover bioequivalence study comparing two 500-mg FORTAMET™ tablets with a single 1000-mg FORTAMET™ tablet. Thirty healthy male subjects were randomized to either a sequence of ABAB or BABA and received either two 500-mg tablets (Tx A) or one 1000-mg tablet (Tx B) immediately after an evening meal. Serial blood samples were then obtained from time zero to 72-hours post-dosing. Average bioequivalence methods were used to analyze the data and the findings are presented in **TABLE 1** and **FIGURE 1**.

TABLE 1: Summary of the PK parameters of plasma metformin for treatments A and B (study 155-116)

Parameter	Unit	Tx A	Tx B	PE*	90% Confidence Intervals*	
					Low	High
C_{max}	ng/mL	1086.66 ± 254.97	1119.03 ± 267.64	97.69	91.35	104.47
AUC_{0-t}	ng*hr/mL	10904.11 ± 2546.14	10848.14 ± 2473.16	100.70	95.19	106.53
AUC_{0-inf}	ng*hr/mL	11090.36 ± 2621.18	10972.93 ± 2506.18	101.24	95.59	107.22
T_{max}	hr	7.90	6.66	---	---	---
$t_{1/2}$	hr	13.84	12.69	---	---	---

Tx A = 1000-mg (2 x 500-mg) metformin XT administered under fed conditions (test)
Tx B = 1000-mg (1 x 1000-mg) metformin XT administered under fed conditions (reference)
* = calculated after ln-transformation



Since the 90% confidence intervals for the ln-transformed parameters C_{max} (91.35% – 104.47%) and AUC_{0-inf} (95.59% – 107.22%) fall within the regulatory range for bioequivalence, 80% to 125%, then it suggests that two 500-mg metformin XT tablets bioequivalent to one 1000-mg metformin XT tablet when administered under fed conditions, hence they are dosage-form equivalent.

These results are in stark contrast to an earlier study (155-013) submitted with the original NDA in which the point estimates for the bioequivalence parameters, C_{max} and AUC, were between [redacted]. However, this earlier study was conducted using product manufactured in pilot batches – the current study used product from scale-up lots (500-mg – 266R021; 1000-mg – 271R021).

Bioanalytical Assay

Metformin levels were measured for all pharmacokinetic studies at [redacted]
Sample extracts were analyzed by [redacted] This method was validated for metformin over the concentration range of [redacted] ng/mL to [redacted] ng/mL for plasma samples.

A pre-study validation run was conducted to verify system performance, calibration standard, and quality control pool preparation, prior to the analysis of study samples. Matrix stability of metformin in human plasma was evaluated by analysis of quality control samples stored under the same conditions as study samples.

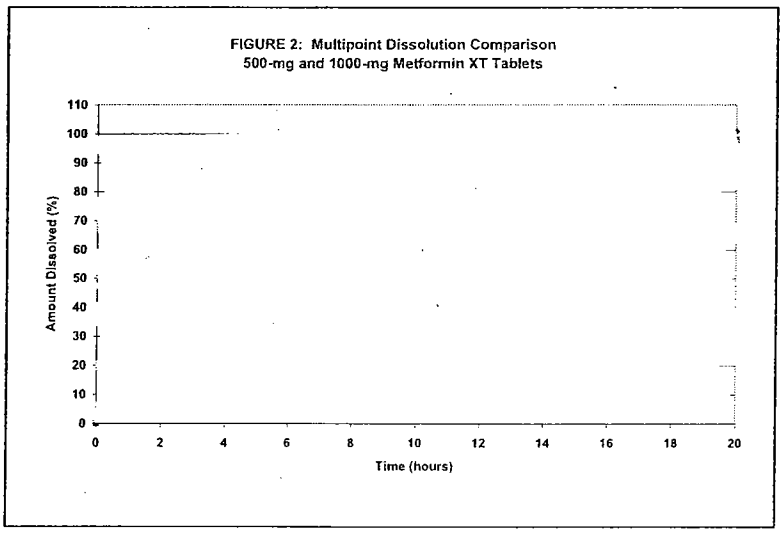
Samples were analyzed in analytical runs, which consisted of a reagent blank, matrix blank, calibration standards, quality controls, and a set of subject samples. Assay precision and accuracy were determined by replicate analyses of human plasma quality control pools prepared at three concentrations spanning the calibration range. Precision was measured as the percent coefficient of variation of the set of values determined for each pool (92% – 95%). Accuracy was expressed as the percent difference of mean value for each pool from the theoretical concentration (97.5% - 99.5%).

Dissolution

In addition to the dosage-form equivalence study, the sponsor also conducted a multipoint dissolution study on the study test lots 266R021 and 271R021, for the 500-mg and 1000-mg tablets, respectively. The proposed dissolution method, and the method used for this evaluation, is described in **TABLE 2**. Results of this study are presented in **FIGURE 2**.

TABLE 2: Proposed Dissolution Method for FORTAMET™ 500-mg and 1000-mg Tablets

Apparatus		USP Apparatus 1 (basket) [redacted]
Medium		0.05M [redacted] buffer, pH [redacted]
Volume		900 ml
Temperature		37° C
Speed		[redacted] RPM
Specification	**500 mg**	2 hr: NMT [redacted], 8 hr: [redacted], 16 hr: NLT [redacted]
	1000 mg	2 hr: NMT [redacted] 8 hr: [redacted] 16 hr: NLT [redacted]



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