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**APPLICATION NUMBER**

**NDA 21-574**

**Clinical Pharmacology and Biopharmaceutics  
Review**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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

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## 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

- The proposed dissolution medium, pH 6.8 phosphate 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:

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

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

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

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

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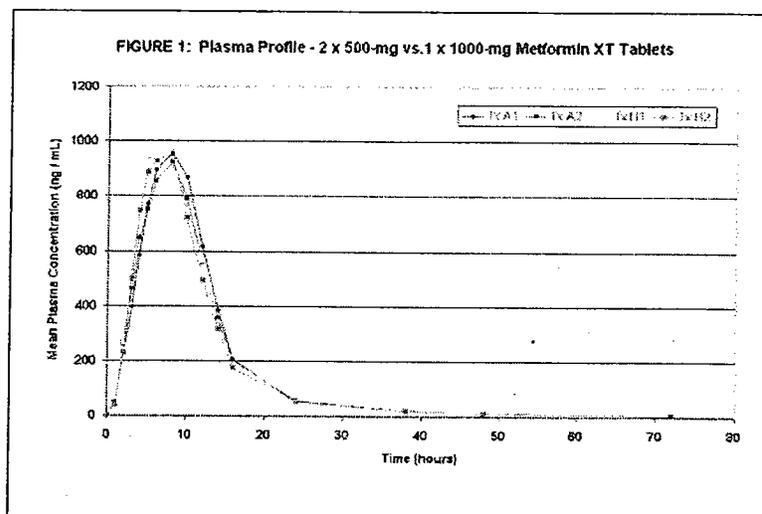
# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

## 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.

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 C 1  
 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).

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

## 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.

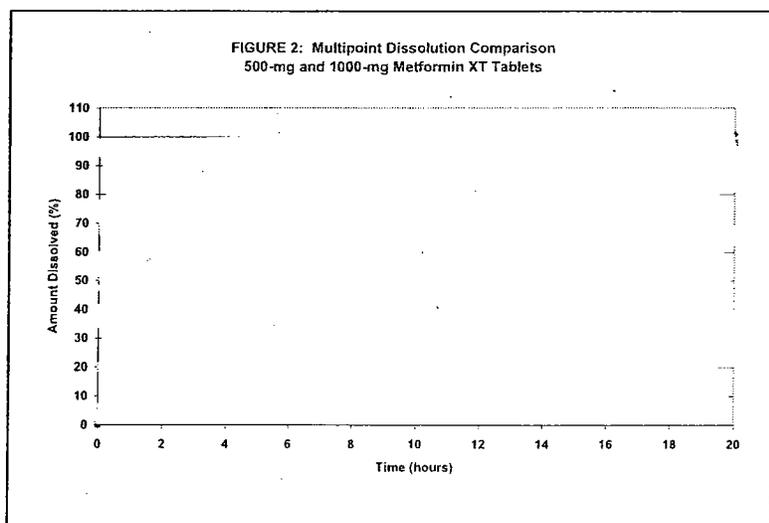
A pre-study validation run was conducted to verify system performance, calibration standard, and quality control pool preparation, prior to the analysis of study samples. Matrix stability of metformin in human plasma was evaluated by analysis of quality control samples stored under the same conditions 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)
Medium	0.05M [redacted] buffer, pH [redacted]
Volume	900 ml
Temperature	37° C
Speed	[redacted] RPM
Specification	500 mg: 2 hr: NMT — 8 hr: — 16 hr: NLT —
	1000 mg: 2 hr: NMT — 8 hr: — 16 hr: NLT —



## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

As stated in the original CPB review by Dr. Wei, "the dissolution condition is apparently independent of pH changes." As a result of this finding, and based on data provided by the sponsor, the dissolution media should be a phosphate buffer at a pH of 6.8. This is in line with all current guidance.

In addition, the release specifications for the 8 hour time point has a [ ] range and is wider than is acceptable for this product. Rather, the sponsor should tighten this range to [ ] and [ ] for the 500-mg and 1000-mg tablets, respectively).

Finally, the third time point at 16 hours is also inappropriate for this product and should be adjusted from not less than (NLT) [ ] to NLT [ ]. **TABLE 3** describes the dissolution method and specifications that appear to be appropriate for this product, given the data provided to the Agency.

TABLE 3: Agency Recommended Dissolution Method for FORTAMET™ 500-mg and 1000-mg Tablets			
<b>Apparatus</b>		USP Apparatus 1 (basket) [ ] 1	
<b>Medium</b>		0.05M [ ] phosphate buffer, pH 6.8	
<b>Volume</b>		900 ml	
<b>Temperature</b>		37° C	
<b>Speed</b>		— RPM	
<b>Specification</b>	<b>500 mg</b>	2 hr: NMT [ ] 8 hr: [ ] 16 hr: NLT [ ]	
	<b>1000 mg</b>	2 hr: NMT [ ] 8 hr: [ ] 16 hr: NLT [ ]	

### Labeling – Clinical Pharmacology Section

NOTE: For recommended labeling changes, please refer to the appendix to this review.

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/s/

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Steve Johnson  
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BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

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NDA: 21-574	Submission Date(s): 12/17/02, 09/30/03
Brand Name	Fortamet™
Generic Name	Metformin extended-release tablets
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Endocrine and Metabolic Drug Products (HFD-510)
Sponsor	Andrx Laboratories
Relevant IND(s)	55,962
Submission Type; Code	505 (b) (2), 1S
Formulation; Strength(s)	Tablets; 500 mg, 1000 mg
Dosing regimen	Start with 1000 mg once a day up to 2500 mg dependent on individual patients' glucose levels
Indication	Type 2 or non-insulin-dependent diabetes mellitus (INDDM)

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## 1 Executive Summary

Andrx Labs, Inc. submitted a 505 (b) (2) NDA for marketing of Fortamet™, an extended release tablets of metformin. The marketed reference drug is an immediate release formulation of metformin hydrochloride (Glucophage®) manufactured by Bristol-Myers Squibb (BMS). BMS also manufactures extended release formulations of metformin HCL, Glucophage® XR, which was approved in 2000 with 500 mg strength. The second strength, 750 mg for Glucophage XR was approved in 2002. However, all comparisons of Fortamet™ relative to the reference drug metformin were made with immediate release forms. All pharmacokinetics/relative bioavailability studies to Glucophage® were performed with pilot lots except for one study with scale-up 1000 mg (Study 155-110). The size of these pilot lots is quite small, [ ] for 500 mg and for about [ ] for 1000 mg, respectively.

The relative bioavailability of Fortamet™ to Glucophage® (immediate release form of metformin HCL) in healthy subjects was compared between Fortamet™ (4 x 500 mg tablets) after breakfast, Fortamet™ (4 x 500 mg tablets) after dinner, and Glucophage® (2 x 500 mg tablets) BID (after breakfast and after dinner). Fortamet™ exhibited extended-release characteristics in terms of pharmacokinetic profiles of metformin when compared to Glucophage®. The relative bioavailability of Fortamet™ given after dinner relative to Glucophage BID was approximately 98%. The bioavailability of Fortamet™ given after breakfast relative to Glucophage was about 80%.

Three additional single dose relative bioavailability studies were conducted with the doses of 1000 mg, 1500 mg and 2500 mg between Fortamet™ and Glucophage. In all three studies, Fortamet™ was given immediately after dinner. The relative bioavailability of Fortamet™ to

Glucophage® at the doses of 1000 mg, 1500 mg and 2500 mg were 1.02, 1.03 and 0.96, respectively.

The steady state pharmacokinetics of Fortamet™ was compared to Glucophage® after 4 weeks of treatment in type 2 diabetic patients. Patients took Fortamet™ (2 x 1000 mg tablets) orally immediately after dinner or Glucophage® (1 x 1000 mg tablet) BID orally immediately after breakfast and after dinner. The results showed that the ratio of AUC<sub>0-24 hr</sub> was about 98%.

Food increases the bioavailability of Fortamet™ by 60% after a single oral dose of 2500 mg was given to healthy male volunteers compared to overnight fasting.

Two scale-up dosage forms, 500 mg and 1000 mg were used in phase 3 clinical trials. The firm conducted one dosage equivalence study for 500 mg and 1000 mg tablets using two pilot lots, which failed on bioequivalence criteria. The firm has not conducted dosage equivalence studies between scale-up lots or commercial formulations although the firm has proposed to market 500 mg and 1000 mg tablets.

In order to improve manufacturability, the formulation composition and manufacturing process have been modified after the phase 3 pivotal clinical trials. The formulation composition increased in [ ] level by [ ] of the total formulation. Subsequently, some manufacturing processes have been modified. All these changes are considered as Level 1 changes according to the SUPAC-MR guidance.

### 1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the original NDA 21-574 for Fortamet™ in the section of human pharmacokinetics and biopharmaceutics. OCPB has found that there is deficiency in that the dosage form equivalence between 500 mg and 1000 mg tablets has not been established. From the perspectives of clinical pharmacology and biopharmaceutics, the 1000 mg tablet is acceptable. However, there is no adequate information about the 500 mg tablet. Therefore, the 500 mg tablet can not be approved at the present time.

For dissolution specifications, the Agency has the following recommendation for 1000 mg tablets:

<b>Apparatus type</b>	USP Apparatus-1 [ ]	J
<b>Dissolution medium</b>	0.05M [ ] 7 phosphate buffer, pH 6.8	
<b>Volume of Medium</b>	900 ml	
<b>Temperature of medium</b>	37°C	
<b>Speed of rotation</b>	~ RPM	
<b>Specification</b>	1000 mg	2 hr: NMT ~ 8 hr: ~ 16 hr: NLT ~

These recommendations and the reviewer's comments and labeling changes should be sent to the sponsor as appropriate.

### Reviewer's Comments:

- 1) There are no dosage form equivalence studies between 500 mg and 1000 mg tablets from scale-up or commercial lots. The firm did perform a dosage form equivalence study for 500 mg and 1000 mg tablets from two pilot formulation lots, in which the bioavailability of 2X500 mg was about 22% less than 1X1000 mg tablets based on the AUC assessment. The dosage form

equivalence between 500 mg and 1000 mg using either scale-up or commercial formulations should be performed.

**Clinical Pharmacology and Biopharmaceutics Briefing** was held on October 6, 2003. The following staff attended the Briefing: Drs. Hank Malinowski, John Hunt, Arzu Selen, Hae-Young Ahn, Raman Raweja, He Sun, Sang Chung and Robert Misbin.

## 1.2 Phase IV Commitments

N/A

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## 3 Summary of CPB Findings

### Pharmacokinetics

#### • Relative bioavailability after single dose:

The relative bioavailability of Fortamet™ to Glucophage® in healthy subjects was compared for the following scheme: Group A received Fortamet™ (4 x 500 mg tablets) immediately after breakfast; Group B received Fortamet™ (4 x 500 mg tablets) immediately after dinner; and Group C received Glucophage® (2 x 500 mg tablets) immediately after breakfast, and immediately after dinner. Fortamet™ exhibited extended-release characteristics in terms of pharmacokinetic profiles of metformin when compared to Glucophage®. The relative bioavailability of Fortamet™ given after dinner relative to Glucophage BID was approximately 98%. The bioavailability of Fortamet™ given after breakfast was lower than Fortamet™ given after dinner or Glucophage given BID (about 80%). The total exposure of Fortamet™ given immediately after dinner was comparable to Glucophage BID dosing with the same dose. This study laid a basis for the further clinical pharmacology biopharmaceutics studies to be given after dinner.

Three additional single dose relative bioavailability studies were conducted with the doses of 1000 mg, 1500 mg and 2500 mg between Fortamet™ and Glucophage. The relative bioavailability of Fortamet™ given after dinner to Glucophage® at the doses of 1000 mg, 1500 mg and 2500 mg were 1.02, 1.03 and 0.96, respectively.

#### • Relative bioavailability after multiple doses:

The steady state pharmacokinetics of Fortamet™ was compared with Glucophage® after 4 weeks of treatment in type 2 diabetic patients. Patients took Fortamet™ (2 x 1000 mg tablets) orally immediately after dinner or Glucophage® (1 x 1000 mg tablet) BID orally immediately after breakfast and after dinner. The results showed that the ratio of AUC<sub>0-24 hr</sub> for equivalent doses of Fortamet™ administered qd and Glucophage® administered bid was about 98%.

- **Dose proportionality:**

A dose proportionality study of Fortamet™ at the dosage levels of 1000, 1500, 2000, and 2500 mg in healthy male volunteers was conducted under fed conditions (after dinner). All pairwise comparisons between doses shows significant difference (p<0.05) with respect to dose-normalized C<sub>max</sub>, AUC<sub>0-72 hr</sub>, and AUC<sub>0-inf</sub> except for the comparison between 2000 and 2500 mg. Although dose-associated increase in metformin exposure within the dose range of 1000 mg to 2500 mg was observed, the lack of dose proportionality was concluded. However, the firm's conclusion may not be granted because the dosage equivalence has never been established between 500 mg and 1000 mg tablets and these two dosage forms were mixed in the study.

- **Elimination:**

Following oral administration of 2500 mg Fortamet™ for 14 days in 18 healthy volunteers, the amount of metformin excreted in the urine and renal clearance after oral administration of Fortamet™ on Days 1 and 14 were generally comparable. Mean ± SD values of these parameters at Days 1 and 14 are summarized in the following table:

Day	Collection interval (hrs)	Mean ± SD (N=18)	
		% of metformin dose excreted in the urine	Renal clearance (mL/min)
Day 1	0-24	44.1 ± 33.2	483 ± 97
Day 14	0 - 24	40.9 ± 29.3	542 ± 310
	0 - 48	42.1 ± 29.2	485 ± 264
	0 - 72	43.9 ± 29.4	482 ± 254

- **Food effect:**

The effect of food on the absorption of Fortamet™ after a single oral dose of 2500 mg in healthy male volunteers was assessed. The bioavailability (AUC<sub>0-72 hr</sub>, and AUC<sub>0-inf</sub>) of 2500 mg Fortamet™ taken after breakfast was approximately 160% of that taken after an overnight fast. The results suggested that food increases the bioavailability of Fortamet™. Similar results were also observed for the extended-release dosage form of Glucophage (Glucophage XR), in which the extent of metformin absorption (as measured by AUC) increased by approximately 50% when Glucophage XR was given with food.

- **Analytical assay:**

A [ ] method was used for the measurement of metformin over the concentration range of [ ] ng/mL to [ ] ng/mL with a lower limit of quantitation equal to the lowest calibration level of [ ] ng/mL.

### Biopharmaceutics

- **Formulation and manufacturing changes:**

In order to improve manufacturability, the formulation composition and manufacturing process have been modified after the phase 3 pivotal clinical trials. The formulation composition increased the level by 1% of the total formulation. Subsequently, some manufacturing processes have been modified. All these changes are considered as Level 1 changes according to the SUPAC-MR guidance.

- **Dosage equivalence:**

The firm conducted one dosage equivalence study for 500 mg and 1000 mg tablets from two pilot lots throughout the drug development program. The bioavailability (C<sub>max</sub>, AUC<sub>0-72 hr</sub> and AUC<sub>0-inf</sub>) of metformin after receiving two 500 mg Fortamet™ tablets relative to receiving one 1000 mg tablet was approximately 76-79%. The 90% confidence intervals were not contained in the [80-125%] range. Therefore, bioequivalence between the two dosage strengths from these two pilot lots was not established. The firm has not conducted dosage equivalence studies between scale-up lots or commercial lots although two dosage strengths, 500 mg and 1000 mg are proposed for marketing.

#### 4 QUESTION BASED REVIEW

##### 4.1 GENERAL ATTRIBUTES

- **What are the highlights of the chemistry and physical-chemical properties of the drug substance?**

Fortamet™ is an extended release formulation of metformin HCL. Metformin hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemics and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents.

The empirical formula of metformin hydrochloride is C<sub>4</sub>H<sub>11</sub>N<sub>5</sub>•HCl and its molecular weight is 165.63. Metformin hydrochloride is a white to off-white crystalline powder that is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

- **What are the highlights of the formulation of drug product?**

The composition of formulations has been modified frequently. The majority of studies of clinical pharmacology and biopharmaceutics were conducted using pilot formulations. Phase 3 clinical trials were conducted with scale-up formulations. The firm has commercial formulation for the to-be-marketed drug products. The scale-up (phase 3) and to-be-marketed formulations have the same composition qualitatively and quantitatively except for the amount of C. The composition and comparison among these formulations is summarized in Table 1 and Table 2 for Fortamet™ 500 mg and 1000 mg tablets, respectively.

**Table 1. Formulation comparison of Fortamet™ 500 mg tablets**

		Fortamet™ 500 mg
--	--	------------------

Components	Function	Pilot Lot P99148 (phase 1)	Scale-up Lot 266R003 (phase 3)		Commercial formulation	
		% w/w	% w/w	mg/tablet	% w/w	mg/tablet
Metformin hydrochloride, BP	Active			500.00		500.00
Sodium lauryl sulfate, NF						
<u>Povidone K-90</u> , USP						
Magnesium stearate, NF						
Cellulose acetate, NF						
Triacetin, USP						
Polyethylene Glycol 400, NF						
Candelilla Wax						

Table 2. Formulation comparison of Fortamet™ 1000 mg tablets

Components	Function	Fortamet™ 1000 mg				
		Pilot Lot P99218 (phase 1)	Scale-up Lot 271R002 (phase 3)		Commercial formulation	
		% w/w	% w/w	mg/tablet	% w/w	mg/tablet
Metformin hydrochloride, BP	Active			1000.00		1000.00
Sodium lauryl sulfate, NF						
<u>Povidone K-90</u> , USP						
Magnesium stearate, NF						
Cellulose acetate, NF						
Triacetin, USP						
Polyethylene Glycol 400, NF						
Candelilla Wax						

- What is the proposed mechanism of drug action and the therapeutic indications?

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see PRECAUTIONS) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting plasma insulin levels and day-long plasma insulin response may actually decrease.

- **What is the proposed dosage and route of administration?**

The firm has proposed two strengths, 500 mg and 1000 mg tablets for extended release formulation. The drug is recommended to start with 1000 mg once a day and titrate up to 2500 mg once a day based on blood glucose levels. The drug is instructed to take with food after evening dinner.

#### 4.2 GENERAL CLINICAL PHARMACOLOGY

- **What is bioavailability of Fortamet™ relative to Glucophage® after a single dose?**

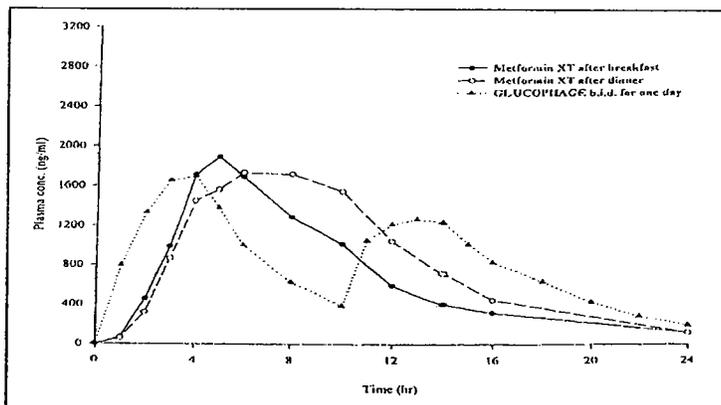
The firm has conducted 4 single dose and 2 multiple dose relative bioavailability studies in comparison with Glucophage®.

Study 155-002 (Lot No. P98231) was an open-label, single-dose, randomized, three-period crossover design with a one-week washout period between treatments and was conducted to compare the extended-release dosage form of metformin (Fortamet™) with Glucophage® in healthy subjects in terms of safety and plasma profile of metformin. In each study period, either a single oral dose of Fortamet™ or BID doses of Glucophage® was administered according to the following scheme: Group A received Metformin XT (4 x 500 mg tablets) immediately after breakfast; Group B received Metformin XT (4 x 500 mg tablets) immediately after dinner; and Group C received Glucophage® (2 x 500 mg tablets) at approximately 8 a.m., immediately following breakfast, and at immediately after dinner. Five male and seven female adult subjects enrolled and completed the study. Results are summarized in the Table 3.

**Table 3. Human pharmacokinetics and bioavailability**

Parameter	Mean ± SD (N=12)			Geometric Mean Ratio (Metformin XT/Glucophage)	
	Fortamet™ after breakfast	Fortamet™ after dinner	Glucophage BID	Fortamet™ after breakfast	Fortamet™ after dinner
<b>C<sub>max</sub> (ng/nL)</b>	2127 ± 545	2053 ± 447	1814 ± 302	1.15	1.12
<b>AUC<sub>0-24 hr</sub> (ng.hr/mL)</b>	16274 ± 4607	19670 ± 3.983	20196 ± 4.24	0.79	0.98
<b>AUC<sub>0-inf</sub> (ng.hr/mL)</b>	17.25 ± 4.96	20.34 ± 4.36	21.22 ± 4.50	0.80	0.96
<b>T<sub>max</sub> (hr)</b>	5 ± 1	7 ± 2	4 ± 1	-	-
<b>T<sub>1/2</sub> (hr)</b>	5.7	3.8	2.7	-	-

**Figure 1. Mean plasma concentration-time profiles of metformin, based on dosing time after oral administration of Fortamet™ (4 x 500 mg) or Glucophage® (2 X 500 mg for one day)**



Fortamet™ exhibited extended-release characteristics in terms of pharmacokinetic profiles of metformin when compared to Glucophage®. The relative bioavailability of Fortamet™ given after dinner relative to Glucophage BID was approximately 98%. The bioavailability of Fortamet™ given after breakfast was lower than Fortamet™ given after dinner or Glucophage given BID (about 80%). The C<sub>max</sub> of the test drug dosing after breakfast and dinner was similar to that after dosing with Glucophage BID for one day. The total exposure of Fortamet™ given immediately after dinner was comparable to Glucophage BID dosing with the same dose.

Three additional single dose relative bioavailability studies (Study 155-101, Study 155-102, and Study 155-103) were conducted with the doses of 1000 mg, 1500 mg and 2500 mg between Fortamet™ and Glucophage. In all three studies, Fortamet™ was given immediately after dinner. The relative bioavailability of Fortamet™ to Glucophage® at the doses of 1000 mg, 1500 mg and 2500 mg were 1.02, 1.03 and 0.96, respectively.

- **What is bioavailability of Fortamet™ relative to Glucophage after multiple doses?**

The firm has conducted two multiple-dose bioavailability studies of Fortamet™ relative to Glucophage® during phase 2 clinical trials.

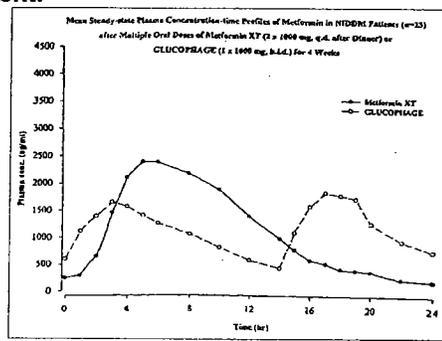
Study 155-005 (Lot No. P99041) was a phase II safety, pharmacokinetic and pharmacodynamic study of Fortamet™ relative to Glucophage® in type 2 diabetic patients. The steady state pharmacokinetics of Fortamet™ was compared with Glucophage® after 4 weeks of treatment. This was a randomized, open-label, two-way crossover study. Eligible patients were randomized to one of the following treatment groups: Study Medication: A - Fortamet™ (2 x 1000 mg tablets) taken orally immediately after dinner; or Study Medication B - Glucophage (1 x 1000 mg tablet) taken orally immediately after breakfast, and immediately after dinner. Period I lasted for 4 weeks, at the completion of which patients received the alternate treatment for 4 weeks in Period II. There was no washout between treatment periods. 24 patients were randomized into Treatment Period. One patient withdrew during Treatment Period I for personal reasons. 23 patients completed the study. The results are presented in Table 4 and Figure 2.

**Table 4. Mean values of pharmacokinetic parameters and bioavailability after dinner relative to Glucophage®**

Treatment	AUC <sub>0-24 hr</sub> (ng.hr/mL)	Cmax (ng/nL)	Tmax (hr)	T <sub>1/2</sub> (hr)	Geometric mean ratio
					AUC <sub>0-24 hr</sub>
Fortamet™	26811 ± 7055	2849 ± 797	6 ± 2	5.4	0.96
Glucophage®	27371 ± 5781	1820 ± 370	3 ± 2	4.4	

The AUC<sub>0-24 hr</sub> for equivalent doses of Fortamet™, administered qd and Glucophage, administered bid, was similar, confirming the extended release nature of Fortamet™. Fortamet™, dosed at 2000 mg qd at 6 PM, was as effective as Glucophage, dosed at 1000 mg bid, for the control of blood sugar in patients diagnosed with NIDDM.

**Figure 2. Pharmacokinetic profiles of Fortamet™ and Glucophage after 4 weeks treatment.**



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Study 155-106 was an identical study except that Fortamet™ was given immediately after breakfast. The relative bioavailability of Fortamet™ to the same dose of Glucophage was 0.84. This is consistent with the result in Study 155-002, in which the relative bioavailability of Fortamet™ after breakfast was lower than that after dinner.

• **What is the dose-concentration relationship for Fortamet™?**

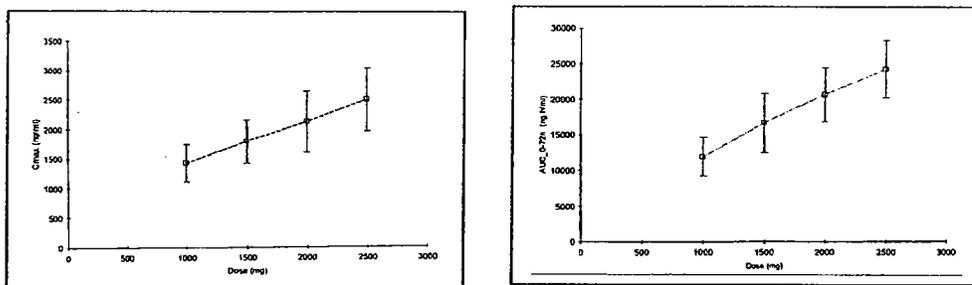
A dose proportionality study of Fortamet™ at the dosage levels of 1000, 1500, 2000, and 2500 mg in healthy male volunteers was conducted under fed conditions (after dinner) (Study 155-106 (Lot No. 271R002 for 1000 mg and Lot No. 266R003 for 500 mg). The pharmacokinetic summary is presented in Table 5 and Figure 3.

**Table 5. Pharmacokinetic parameters of Fortamet™ ranging from 1000 mg to 2500 mg**

Parameter	Fortamet™			
	1000 mg	1500 mg	2000 mg	2500 mg
Cmax (ng/nL)	1424 ± 319	1784 ± 337	2110 ± 517	2483 ± 533
AUC <sub>0-72 hr</sub> (ng.hr/mL)	11900 ± 2763	16677 ± 4140	20646 ± 3816	24179 ± 3971
AUC <sub>0-inf</sub> (ng.hr/mL)	11935 ± 2708	16697 ± 4151	20813 ± 3870	24264 ± 4101
Tmax	6.3 ± 1.4	6.7 ± 1.6	7.8 ± 2.0	7.2 ± 2.1
T <sub>1/2</sub>	5	5.6	7.4	7.5

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**Figure 3. Mean plasma metformin Cmax and AUC<sub>0-72hr</sub> versus dose after a single oral dose of 1000, 1500, 2000 or 2500 mg Fortamet™ after dinner**



All pair-wise comparisons between doses are significant ( $p < 0.05$ ) with respect to dose-normalized Cmax, AUC<sub>0-72 hr</sub>, and AUC<sub>0-inf</sub> except for the comparison between 2000 and 2500 mg. The trend tests are also significant ( $p < 0.01$  for all dose-normalized parameters) indicating that the bioavailability decreases as the dose increases (Table 6).

**Table 6. Summary of pair-wise comparisons**

Dose-normalized parameters	Dose (mg)	Value	p-values of Comparisons with		
			1500 mg	2000 mg	2500 mg
Cmax (ng/nL)	1000	1424 ± 319	0.0001	0.0001	0.0001
	1500	1784 ± 365	-	0.0049	0.0001
	2000	2110 ± 517	-	-	<b>0.2125</b>
	2500	2483 ± 533	-	-	-
AUC <sub>0-72 hr</sub> (ng.hr/mL)	1000	11900 ± 2763	0.0256	0.0001	0.0001
	1500	16677 ± 4140	-	0.0201	0.0001
	2000	20646 ± 3816	-	-	0.0532
	2500	24179 ± 3971	-	-	-
AUC <sub>0-inf</sub> (ng.hr/mL)	1000	11935 ± 2708	0.0213	0.0001	0.0001
	1500	16697 ± 4154	-	0.0329	0.0001
	2000	20813 ± 3870	-	-	<b>0.0532</b>
	2500	24264 ± 4101	-	-	-

**Reviewer's comments:** It is difficult to determine what causes the small lack of dose-proportionality because the dosage-equivalence between 500 mg and 1000 mg tablets from scale-up lots has never been performed or reported. The unequal dosage forms could have contributed to this phenomenon. Therefore, no conclusion can be drawn from this study although we know that the lack of true dose proportionality was observed with Glucophage and Glucophage XR.

- What is the effect of food on the bioavailability of Fortamet™?

Study 155-107 (Lot No. 271R002 for 1000 mg and Lot No. 266R003 for 500 mg) was conducted to assess the effect of food on the absorption of Fortamet™ after a single oral dose of 2500 mg in healthy male volunteers. This was a single-center, single-dose, open-label, randomized, two-period crossover study with a 7 day washout period between treatments. The assigned study periods consisted of one of the following treatment groups: Group A received two 1000 mg Fortamet™ tablets and one 500 mg Fortamet™ tablet immediately after breakfast, and Group B received two 1000 mg Fortamet™ tablets and one 500 mg Fortamet™ tablet after an overnight fast. Twenty-four healthy male subjects enrolled and completed the study. Table 7 is the summary of pharmacokinetics parameters.

**Table 7. Pharmacokinetic parameters, relative bioavailability, and 90% confidence interval after Fortamet given after breakfast and overnight fasting.**

Parameter	Mean ± SD (N=24)		Relative Bioavailability (%)	90% Confidence Interval
	2500 mg Fortamet™ after breakfast	2500 mg Fortamet™ overnight fasting		
Cmax (ng/nL)	1949 ± 629	1504 ± 530	132.1	114.9 – 151.8
AUC <sub>0-72 hr</sub> (ng.hr/mL)	18383 ± 4818	11759 ± 4367	158.5	141.8 – 177.2
AUC <sub>0-inf</sub> (ng.hr/mL)	18862 ± 5096	11238 ± 2543	163.5	145.2 – 184.0
Tmax	6.1 ± 2.3	4.0 ± 1.1	-	-
T <sub>1/2</sub>	8.6	9.3	-	-

The bioavailability (AUC<sub>0-72 hr</sub> and AUC<sub>0-inf</sub>) of 2500 mg Fortamet™ taken after breakfast was approximately 160% of that taken after an overnight fast. The results suggested that food increases the bioavailability of Fortamet™. Similar results were also observed for the extended-release dosage form of Glucophage (Glucophage XR), in which the extent of metformin absorption (as measured by AUC) increased by approximately 50% when Glucophage XR was given with food.

- **What is the bioavailability of Fortamet™ relative to Glucophage® under fasting condition?**

Study 155-110 (Lot No. 271 R002) was conducted to assess the relative bioavailability comparing a single dose of 1000mg Fortamet™ to a single dose of 1000 mg Glucophage in healthy male volunteers under fasting conditions. This was a single-center, single-dose, open-label, randomized, two-period crossover study with a 7 day washout period between treatments. Twenty-four healthy male subjects enrolled and completed the study.

Pharmacokinetic parameters, relative bioavailability, and 90% confidence interval from 24 subjects are summarized in Table 8:

**Table 8. Pharmacokinetic parameters, relative bioavailability, and 90% confidence interval after single dose of 1000 mg under fasting condition**

Parameter	Mean ± SD (N=24)		Relative Bioavailability (%)	90% Confidence Interval
	Fortamet™ (Lot No. 271 R002)	Glucophage (Lot No. MJC83)		
Cmax (ng/nL)	828 ± 361	1854 ± 563	42.6	36.2 – 50.2
AUC <sub>0-72 hr</sub> (ng.hr/mL)	5908 ± 2079	11952 ± 3042	48.3	42.6 – 54.8
AUC <sub>0-inf</sub> (ng.hr/mL)	6401 ± 2102	12514 ± 3086	50.2	43.7 – 57.7
Tmax	4.5 ± 0.8	2.7 ± 0.9	-	-

T <sub>1/2</sub>	7.8	6.0	-	-
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The relative bioavailability (C<sub>max</sub>, AUC<sub>0-72 hr</sub>, and AUC<sub>0-inf</sub>) of a 1000 mg Fortamet™ tablet when compared to a 1000 mg Glucophage® tablet was approximately 50% when both medications were given under fasting conditions to healthy male volunteers. The 90% confidence intervals were outside the [80-125%] range.

This finding is consistent with those of an earlier study which demonstrated that the single- and multiple-dose bioavailability of metformin is generally lower when a sustained release formulation is compared against an immediate-release formulation under fasted conditions. Several other studies have shown that the presence of food decreases metformin bioavailability from Glucophage® immediate-release formulation by 25% but, in contrast, food increases metformin bioavailability from various extended-release metformin formulations (e.g., Glucophage XR, Fortamet™) by approximately 50-60%.

#### 4.3 INTRINSIC FACTORS

##### 5.3.1. Gender

No gender difference was observed from the analyses of pharmacokinetics studies.

**5.3.2. Race, Renal impairment, Hepatic impairment, Pediatric:** No studies were conducted with Fortamet™.

#### 4.4 Extrinsic Factors:

No studies have been conducted with Fortamet™.

#### 4.5 General Biopharmaceutics

- What has been changed in the formulation composition and manufacturing process after the scale-up lots used in pivotal clinical trials?**

In order to improve manufacturability, the formulation composition and manufacturing process have been modified after lots used in the phase 3 pivotal clinical trials. Table 9 summarizes these changes. However, all these changes were Level 1 changes according to the SUPAC-MR guidance.

**Table 9. Changes Made to Improve the Manufacturability (Ruggedness and Reproducibility) of Fortamet™ Tablets, 500mg and 1000mg**

Composition	Type of Change	Level of Change**
Increase [ ] of the total formulation	] level by [ ]	Level 1
<b>Processes</b> Elimination of [ ]	] ]	Level 1
<b>Process</b> Changed [ ]	] ]	Level 1
<b>Process</b> Decrease in [ ]	] ]	Level 1

\*This change applies to 1000 mg Fortamet Tablets only.

\*\*As per "Guidance for Industry. SUPAC-MR: Modified Release Solid Oral Dosage Forms"

Evaluation of the Fortamet™ Tablets with commercial composition/process was further conducted using dissolution testing. Fortamet™ tablets with biobatch composition/process were compared to the Fortamet™ Tablets with the revised composition and process in simulated

intestinal fluid of pH 7.5 at 100 rpm and were found similar. Although the similarity testing (using the f2 metric) of the two dissolution profiles obtained at pH 7.5 were conducted, further dissolution testing was performed in simulated gastric fluid (pH 1.2), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8), which is usually required to justify Level 2 changes. Profiles were also compared at higher agitation of 100 rpm to ensure that changed dosage forms behaves identical at higher motility patterns in the gastrointestinal tract. As per the f-2 metric, the dissolution profiles in various media for the changed drug product and the biobatch were similar as shown in Table 10. **Table 10. Comparison of dissolution profiles of Fortamet™ tablets with the scale-up composition/process vs. commercial composition/process using f2 values**

Fortamet™ Tablet 500 mg			
pH of the Dissolution Medium/Agitation Speed		Lot # 266R003B* (Biobatch)	Lot# 266R021** (Commercial Batch)
pH 1.2;	rpm	Reference	f2 = 81
pH 4.5;	rpm	Reference	f2 = 84
pH 6.8;	rpm	Reference	f2 = 88
pH 7.5;	rpm	Reference	f2 = 60
Fortamet™ Tablet 1000 mg			
		Lot # 271R002B* (Biobatch)	Lot # 271R021A** (Commercial Batch)
pH 1.2;	rpm	Reference	f2 = 68
pH 4.5;	rpm	Reference	f2 = 83
pH 6.8;	rpm	Reference	f2 = 68
pH 7.5;	rpm	Reference	f2 = 67

#Dissolution testing was performed using USP Apparatus I at C

\*Biobatches with the scale-up composition/process.

\*\*Lot # with the revised composition/process.

• **What is the association of pilot and scale-up lots with study protocols?**

During the development of Fortamet™, various lots were used mainly in Phase 1 clinical pharmacology and biopharmaceutical studies. Among these pilot and scale-up lots, the pilot lot and scale-up lots for 1000 mg (P99218 and 271R002) were bioequivalent. For 500 mg, Both Scale-up lots (266R003 and 266R004) were failed to establish bioequivalence to the Pilot Lot P99148. One dosage equivalence study was performed between two pilot lots for 500 mg and 1000 mg (P99148 and P99218) and was failed for bioequivalence criteria, in which 2X500 mg was about 22% less than 1X1000 mg tablet based on the AUC ratio. The dosage equivalence studies between scale-ups and commercial lots have not been conducted.

**Table 11. Fortamet™ lots and study protocol**

Dosage	Lot Type	Lot No./ (Batch size)	Phase 1	Phase 2	Phase 3	
500 mg	Pilot Lot	P98231	155-002 155-003 155-004	-	-	
		P99148	155-013 155-103 155-104 155-109	-	-	
		Scale-up	266R003	155-104 155-106 155-107 155-108	-	155-301 155-302
		266R004	155-109	-	-	
	1000 mg	Pilot Lot	P99041	-	155-005	-
			P99218	155-013 155-101 155-102 155-103 155-105	155-006	-

	Scale-up	271R002 [       ]	155-105 155-106 155-107 155-108 155-110	-	155-301 155-302
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Note: Lots in red were used for bioequivalence studies.

- What is the outcome of bioequivalent studies between Pilot Lot P99148 and Scale-up Lot 266R003/004 for 500 mg strength?

Two bioequivalence studies were performed to determine if pilot Lot 99148 is bioequivalent to two Scale-up Lots 266R003 (Table 12) and 266R004 (Table 13). Study 155-104 was conducted to assess the bioequivalence comparing two lots of 500 mg Fortamet™ tablets in healthy volunteers: a scale-up lot relative to a pilot lot of 500 mg Fortamet™ tablet under fed conditions (after dinner).

**Table 12. Pharmacokinetic parameters of pharmacokinetic parameters, relative bioavailability, 90% confidence interval**

Parameter	Mean ± SD (N=24)		Relative Bioavailability (%)	90% Confidence Interval
	Fortamet™ Lot 266R003 (Scale-up)	Fortamet™ Lot P99148 (Pilot)		
Cmax (ng/nL)	642 ± 263	751 ± 295	83.4	72.0– 96.8
AUC <sub>0-72 hr</sub> (ng.hr/mL)	5793 ± 2264	6471 ± 2434	88.9	78.2– 101.0
AUC <sub>0-inf</sub> (ng.hr/mL)	5782 ± 2221	6687 ± 4772	86.0	74.8– 98.8
Tmax	6.3 ± 1.6	5.8 ± 1.6	-	-
T <sub>1/2</sub>	4.2	3.8	-	-

**Table 13. Pharmacokinetic parameters, relative bioavailability, and 90% confidence interval**

Parameter	Mean ± SD (N=24)		Relative Bioavailability (%)	90% Confidence Interval
	Fortamet™ Lot 266R004 (Scale-up)	Fortamet™ Lot P99 148 (Pilot)		
Cmax (ng/nL)	749 ± 293	695 ± 301	109.0	94.3 – 125.9
AUC <sub>0-72 hr</sub> (ng.hr/mL)	6564 ± 2074	5951 ± 2235	113.2	100.0 – 128.1
AUC <sub>0-inf</sub> (ng.hr/mL)	6479 ± 2035	5553 ± 2197	123.0	108.1 – 139.8
Tmax	6.6 ± 1.8	5.8 ± 1.5	-	-
T <sub>1/2</sub>	3.5	3.8	-	-

The bioavailability (Cmax, AUC<sub>0-72 hr</sub>, and AUC<sub>0-inf</sub>) of metformin after receiving one 500 mg Fortamet™ tablet, Lot 266R003 (scale-up lot), relative to receiving one 500 mg Fortamet™ tablet, Lot No. P99 148 (pilot lot), was approximately 83-89%. The 90% confidence intervals were not contained in the [80-125%] range. The bioavailability (Cmax, AUC<sub>0-72 hr</sub>, and AUC<sub>0-inf</sub>) of metformin Lot 266R004 (a scale-up lot), relative to receiving one 500 mg Metformin XI tablet, Lot P99148 (a pilot lot), was approximately 109-123%. The 90% confidence intervals were not contained in the [80-125%] range for both studies. Therefore, the bioequivalence between the scale-ups and pilot lots for 500 mg was not established.

- What is the outcome of bioequivalent study between Pilot Lot P99218 and Scale-up Lot 271R002 for 1000 mg strength?

Study 155-105 (Lot No. 271R002 and Lot No. P99218) was conducted to assess the bioavailability of a scale-up lot of 1000 mg Fortamet™ tablets relative to a pilot lot of 1000 mg Fortamet™ tablets under fed conditions (after dinner) in healthy volunteers to see if they are bioequivalent. Twenty-four healthy male subjects enrolled and 23 subjects completed the study.

**Table 13. Pharmacokinetic parameters of pharmacokinetic parameters, relative bioavailability, 90% confidence interval**

Parameter	Mean ± SD (N=24)		Relative Bioavailability (%)	90% Confidence Interval
	Fortamet™ Lot 271R002 (Scale-up)	Fortamet™ Lot P99218 (Pilot)		
C <sub>max</sub> (ng/nL)	1541 ± 348	1682 ± 337	91.0	83.9– 98.8
AUC <sub>0-72 hr</sub> (ng.hr/mL)	12824 ± 2348	13518 ± 2225	94.5	89.9– 99.3
AUC <sub>0-inf</sub> (ng.hr/mL)	13169 ± 2007	13747 ± 2253	94.5	89.4– 99.9
T <sub>max</sub>	5.3 ± 1.1	5.3 ± 0.9	-	-
T <sub>1/2</sub>	6.7	6.2	-	-

The bioavailability (C<sub>max</sub>, AUC<sub>0-72 hr</sub>, and AUC<sub>0-inf</sub>) of metformin after receiving one 1000 mg Fortamet™ tablet, Lot 271R002 (a scale-up lot), relative to receiving one 1000 mg Fortamet™ tablet, Lot P99218 (a pilot lot), was approximately 91-95%. The 90% confidence intervals were contained in the [80 -125%] range, therefore; bioequivalence between these two lots was demonstrated.

- **Has the dosage equivalence been established between 500 mg and 1000 mg?**

The firm conducted one dosage equivalence study for two pilot lots throughout the drug development program. Study 155-013 was a single-dose bioequivalence study of two dosage strengths of 500 mg and 1000 mg Fortamet™ from two strength pilot lots (P99218, pilot lot for 1000 mg and P99148, pilot lot for 500 mg) in healthy male volunteers. The objective of this study was to determine if one 1000 mg Fortamet™ tablet and two 500 mg Fortamet™ tablets are bioequivalent under overnight fasting conditions in healthy subjects. This was a single-center, open-label, single-dose, randomized, two-period crossover study with a three-week washout period between treatments. A total of 24 healthy male volunteers completed the study.

**Table 14. Pharmacokinetics summary**

Parameter	Mean ± SD (N=24)		Relative Bioavailability (%)	90% Confidence Interval
	One 1000 mg Tablet	Two 500 mg Tablets		
C <sub>max</sub> (ng/nL)	1275 ± 411	956 ± 325	75.8	67.5 – 85.1
AUC <sub>0-72 hr</sub> (ng.hr/mL)	9010 ± 2549	7048 ± 2209	78.5	70.4 - 87.6
AUC <sub>0-inf</sub> (ng.hr/mL)	8991± 2566	7281± 2023	77.7	67.4 - 89.6
T <sub>max</sub>	4 ± 1	4 ± 1	-	-
T <sub>1/2</sub>	8.7	8.6	-	-

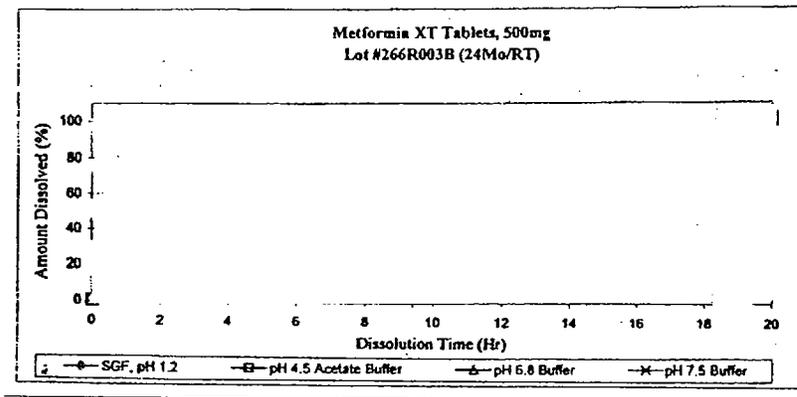
The bioavailability (C<sub>max</sub>, AUC<sub>0-72 hr</sub> and AUC<sub>0-inf</sub>) of metformin after receiving two 500 mg tablets relative to receiving one 1000 mg tablet was approximately 76-79%. Therefore, bioequivalence between the two dosage strengths from these two pilot lots was not established. The firm has not conducted dosage equivalence studies between scale-up lots or commercial lots although two dosage strengths, 500 mg and 1000 mg are proposed for market.

• **What are the proposed dissolution method and specification?**

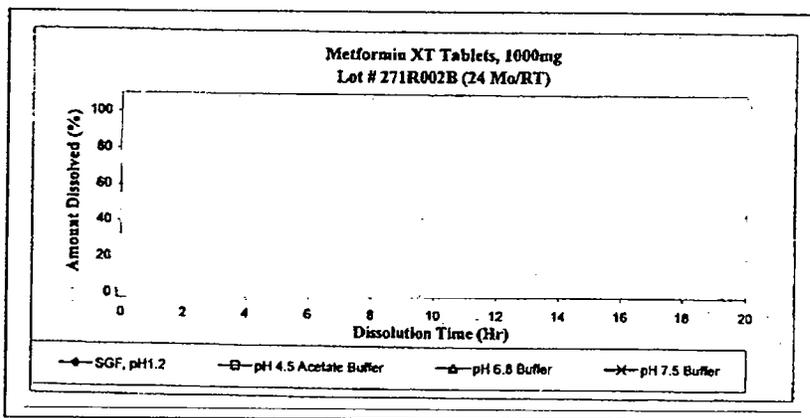
The dissolution release of Fortamet™ Tablets, 500 mg (lot # 266R003B) and 1000 mg (lot # 271R002B) in various dissolution media i.e. simulated gastric fluid (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8) and artificial intestinal fluid (pH 7.5) was studied as seen from these figures.

During the development of dissolution method for Fortamet™, various aqueous media was evaluated. Figures 4 and 5 show that the dissolution profiles are almost superimposed when different media (pH 1.2, 4.5, 6.8, and 7.5) was applied.

**Figure 4. Effect of Medium pH on the Dissolution Profiles of Fortamet™ Tablets, 500mg**



**Figure 5. Effect of Medium pH on the Dissolution Profiles of Fortamet™ Tablets, 1000mg**



The firm has proposed the following dissolution specifications:

**Table 15. Proposed dissolution method and specifications**

<b>Apparatus type</b>	USP Apparatus- L			
<b>Dissolution medium</b>	0.05M [ ] buffer, pH [ ]			
<b>Volume of Medium</b>	900 ml			
<b>Temperature of medium</b>	37°C			
<b>Speed of rotation</b>	~ RPM			
<b>Specification</b>	<b>500 mg</b>	2 hr: NMT [ ]	[ ] 8 hr [ ]	[ ] 16 hr: NLT [ ]
	<b>1000 mg</b>	2 hr: NMT [ ]	[ ] 8 hr [ ]	[ ] 16 hr: NLT [ ]

**Reviewer's comments:** The dissolution condition is apparently independent of pH changes. Specifications for 8 hour time point with [ ] range are wider than the Agency generally accepts, which should be kept within [ ] window. The third time point at 16 hours seems too loose, at which the drug products have been dissolved already for a while. This reviewer recommends the modification for interim dissolution method and specifications as follows: pH 6.8, specifications at 8 hours: [ ] for 500 mg and [ ] for 10000 mg, at 12 hours, not less than [ ]

#### 4.6 Analytical

- **What is the property of analytical method?**

Metformin levels were measured for all pharmacokinetic studies at [ ] Sample extracts were analyzed by [ ] This method has been validated for metformin over the concentration range of [ ] ng/mL to [ ] ng/mL for plasma samples and over the concentration range of [ ] ng/mL to [ ] ng/mL with a lower limit of quantitation equal to the lowest calibration level of [ ] ng/mL for urine 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 [ ] Accuracy was expressed as the percent difference of mean value for each pool from the theoretical concentration [ ]).

### 5 LABELING RECOMMENDATIONS

#### LABELING COMMENTS:

It will be deferred until the required dosage form equivalence study is reviewed.

### 6 Appendix: Table: Fortamet™ Lots and Study Protocols

**Table. Summary of Fortamet™ Lots and Study Protocols (BA Studies relative to Glucophage in red!)**

Dosage	Lot Type	Lot No./ (Batch size)	Phase 1	Phase 2	Phase 3
	Pilot Lot	P98231 [ ]	155-002: SD: 4X500mg – a) after BF b) after dinner c) Glucophage (2X500mg) BID  155-003: MD: (4X500mg) X 14 days – Day 1 and Day 14: no difference in PK.  155-004: MD: (2X500mg) BID X 14 days. Day 1 and Day 14: no difference in PK.		

500 mg		P99148 —	<p>155-013: BE study: 2X500 mg/pilot 99148 Vs. 1X1000mg/pilot 99218—failed. AUC: 78%</p> <p>155-103: SD: 2X1000mg+1X500mg Fortamet/pilot lots Vs. Glucophage 1000mg BF + 1500mg Dinner—AUC:0.96</p> <p>155-104: BE study: 2X500mg/scale-up 266R003 Vs 1X500mg/pilot 99148, failed.</p> <p>155-109: BE study: 1X500mg/scale-up 266R004 Vs 1X500mg/pilot 99148, failed.</p>	-	-
	Scale-up	266R003 —	<p>155-104: BE study: 2X500mg/scale-up 266R003 Vs 2X500mg/pilot 99148, failed.</p> <p>155-106: dose proportionality study: not proportional/non-linear</p> <p>155-107: Food effect: 2X2000mg +1X500mg: after BF Vs. overnight fasting: AUC:1.59</p> <p>155-108: MD:2X1000mg +1X500mg/scale-up lots X 14 days: comparable bet/ Day 1 and Day14.</p>	-	155-301 155-302
		266R004 —	155-109: BE study: 1X500mg/scale-up 266R004 Vs 1X500mg/pilot 99148, failed.	-	-
1000 mg	Pilot Lot	P99041 —		155-005 MD: (2X1000mg) Vs. Glucophage 1000mg BiD X 4wks AUC:0.96	-
		P99218 —	<p>155-013: BE study: 2X500 mg/pilot 99148 Vs. 1X1000mg/pilot 99218—failed. AUC: 78%</p> <p>155-101: SD: 1X1000mg Fortamet Vs. Glucophage 500mg BID—AUC:1.02</p> <p>155-102: SD:1X1000mg+1X500mg Fortamet/pilots lots Vs. Glucophage 500mg BF+1000mg dinner —AUC:1.03</p> <p>155-103:SD: 2X1000mg+1X500mg Fortamet/pilot lots Vs. Glucophage 1000mg BF + 1500mg Dinner—AUC:0.96</p> <p>155-105: BE study: 1X1000mg/scale-up 271R002 Vs 1X1000mg/pilot 99218, Pass!!</p>	155-006 identical to 005 except given after BF for Fortamet AUC:0.80	-
	Scale-up	271R002 —	<p>155-105: BE study: 1X1000mg/scale-up 271R002 Vs 1X1000mg/pilot 99218, Pass!!</p> <p>155-106: dose proportionality study: not proportional/non-linear</p> <p>155-107: Food effect: 2X2000mg +1X500mg: after BF Vs. overnight fasting: AUC:1.59</p> <p>155-108:MD: 2X1000mg +1X500mg/scale-up lots X 14 days: comparable bet/ Day 1 and Day14</p> <p>155-110: SD: 1X1000mg Fortamet Vs. 1X1000 mg Glucophage—AUC:0.48</p>	-	155-301 155-302

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**Office of Clinical Pharmacology and Biopharmaceutics**  
**New Drug Application Filing and Review Form**

**General Information About the Submission**

<b>NDA Number</b>	21-574	<b>Brand Name</b>	Fortamet ER
<b>OCPB Division (I, II, III)</b>	DPE II	<b>Generic Name</b>	Metformin HCL ER
<b>Medical Division</b>	HFD-510	<b>Drug Class</b>	
<b>OCPB Reviewer</b>	Xiaoxiong (Jim) Wei	<b>Indication(s)</b>	Diabetes, NIDDM
<b>OCPB Team Leader</b>	Hae-Young Ahn	<b>Dosage Form</b>	Tablets
		<b>Dosing Regimen</b>	500 mg 1000 mg
<b>Date of Submission</b>	12-17-02	<b>Route of Administration</b>	P.O.
<b>Estimated Due Date of OCPB Review</b>	09-01-03	<b>Sponsor</b>	Andrx Labs., Inc.
<b>PDUFA Due Date</b>	10-19-03	<b>Priority Classification</b>	S1
<b>Division Due Date</b>	10-01-03		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	X	5		
multiple dose:	X	2		
<b>Patients-</b>				
single dose:				
multiple dose:	X	2		
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	4		
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>	X	2		
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		16		
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<b>Application filable ?</b>	YES			
<b>Comments sent to firm ?</b>	NO			

**Briefing In Content:**

The sponsor, Andrx Labs, Inc. has submitted their NDA for Fortamet™ for the treatment of type 2 diabetes as a 505(b)2 application. Fortamet™ is extended release forms of metformin HCL. The sponsor conducted 16 human pharmacokinetic studies and two pivotal clinical trials. The proposed marketing dosage strengths are 500 mg and 1000 mg tablets. The proposed dosing schedule is to start with 1000 mg once daily with the evening meal. Dosage increases will be made in increments of 500 mg weekly up to a maximum of 2500 mg once daily. The major problem is that the sponsor failed to establish the bioequivalence between the scale-up vs. pilot formulations for 500 mg tablets. And furthermore the sponsor failed to establish dosage form equivalence between the 1000 mg and 500 mg tablets. The detailed information is described below.

**(Study 155-104 (fed condition):**

BE study: two formulations of 2X 500 mg Metformin XT: scale-up lot (Lot No. 266R003) vs. pilot lot (Lot No. P99148).

Results: 90% CI: (72%, 96.8%), (78.2%, 101.2%) and (74.8% and 98.8%) for Cmax, AUC 0-72h, AUC 0-inf.

✓ **Study 155-105 (fed condition):**

BE: scale-up formulation vs. pilot formulation for 1000 mg tablets: **pass**.

✓ **Study 155-013 (fast condition):**

BE 1X 1000 mg vs. 2X 500 mg Metformin XT under following overnight fast.

Results: Relative F (2X500/1X1000mg): 90% CI: (67.5%, 85.1%), (70.4%, 87.6%) and (67.4.8% and 89.6%) for Cmax, AUC 0-72h, AUC 0-inf.

✓ **Study 155-109 (fed condition):**

BE study: two formulations of 2X 500 mg Metformin XT: scale-up lot (Lot No. 266R004, scale-up lot, not used in pivotal clinical trials) vs. pilot lot (Lot No. P99148).

Results: Relative F (scale-up/pilot): 109.0%, 113.2%, and 123% for Cmax, AUC 0-72h, AUC 0-inf.

✓ **Pivotal Clinical trials:**

✓ **155-301:** dose groups: 1000, 1500, 2000, 2500 mg titrated up or down in 500-mg increments.

Formulations used:

MET 500 mg tablet (Lot No. 266R003, **scale-up lot**)

MET 1000 mg tablet (Lot No. 271R002, **scale-up lot**)

MET PBO 500 mg tablet (Lot No. 266R001, **scale-up lot**)

MET PBO 1000 mg tablet (Lot No. 271R001, **scale-up lot**)

✓ **155-302:** dose groups: 2000 and 2500 mg.

Formulations used:

MET 500 mg tablet (Lot No. 266R003, **scale-up lot**)

MET 1000 mg tablet (Lot No. 271R002, **scale-up lot**)

MET PBO 500 mg tablet (Lot No. 266R001, **scale-up lot**)

MET PBO 1000 mg tablet (Lot No. 271R001, **scale-up lot**)

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/s/

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Xiao-xiong Wei  
2/11/03 04:50:15 PM  
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Hae-Young Ahn  
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