

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-574**

**Administrative/Correspondence Reviews**

**EXCLUSIVITY SUMMARY for NDA # 21-574 SUPPL # N/A**

**Trade Name: Fortamet Generic Name: Metformin HCl extended-release) Tablets**

**Applicant Name: Andrx HFD-510**

**Approval Date: April 27, 2004**

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Application contains only BE studies.

d) Did the applicant request exclusivity?

YES // NO //

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES // NO //

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES // NO //

(NDA 21-202 Glucophage XR from BMS is 500 mg and 750 mg only. NDA 21-574 is 500 mg and 1000 mg).

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES // NO //

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES // NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 21-202 Glucophage XR from BMS

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES // NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES // NO /\_\_\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO //

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO //

If yes, explain:

- (c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study 301

Investigation #2, Study 302

Investigation #3, Study 303

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 301	YES /___/	NO /✓/
Investigation #2 302	YES /___/	NO /✓/
Investigation #3 303	YES /___/	NO /✓/



Investigation #3

IND 55,962 YES // ! NO /\_\_\_/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /\_\_\_/ Explain NA ! NO /\_\_\_/ Explain \_\_\_\_\_

Investigation #2

YES /\_\_\_/ Explain NA ! NO /\_\_\_/ Explain \_\_\_\_\_

Investigation #3

YES /\_\_\_/ Explain NA ! NO /\_\_\_/ Explain \_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/ NO //

If yes, explain: \_\_\_\_\_

Jena Weber  
DFS

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/s/

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David Orloff  
4/28/04 05:20:48 PM

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center For Drug Evaluation and Research

DATE: April 28, 2004

FROM: David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-574  
Fortamet (metformin HCl)  
Andrx Labs

SUBJECT: NDA review issues and recommended action

**Background**

This is a brief memorandum at the time of approval of this NDA. It is in follow up to my memo of October 17, 2003 addressing the first cycle review of this application for a long-acting form of metformin. On the first cycle, the principal deficiency was the failure to provide sufficient data to support dosage form equivalence of the 500 mg and 1000 mg tablets. In addition, a number of labeling comments were made.

A December 19, 2003, submission constituted a complete response to the first action letter. The Biopharmaceutics issues were adequately addressed and OCPB at that time recommended approval of the 500 mg dosage strength (to accompany the previously recommendation to approve the 1000 mg dosage strength). A second AE letter was issued on February 20, 2004, citing incomplete patent certifications related to Glucophage XR.

A February 26, 2004 submission constituted a complete response to the second action letter.

All issues have been addressed. The labeling has been negotiated to final, acceptable form.

**Recommendation**

This application may be approved.

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/s/

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David Orloff  
4/28/04 05:19:19 PM  
MEDICAL OFFICER

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-574		
Drug: Fortamet (metformin HCl extended-release) Tablets	Applicant: Andrx	
RPM: J.Weber	HFD-510	Phone # 76422
Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:		
• Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
• Chem class (NDAs only)	3	
• Other (e.g., orphan, OTC)	N/A	
❖ User Fee Goal Dates	April 27, 2004	
❖ Special programs (indicate all that apply)	<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	
❖ User Fee Information		
• User Fee #4435	<input checked="" type="checkbox"/> Paid	
• User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
• User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)	N/A	
• OC clearance for approval	April 23, 2004 (e-mail via Liz Dickinson).	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	<input checked="" type="checkbox"/> Verified	
❖ Patent		
• Information: Verify that patent information was submitted	<input checked="" type="checkbox"/> Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input checked="" type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	<input checked="" type="checkbox"/> Verified	
❖ Exclusivity Summary (approvals only)	<input checked="" type="checkbox"/>	

❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	✓
<b>General Information</b>	
❖ Actions	
• Proposed action	(✓) AP ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE letters issued 10/17/03 and 2/20/04
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	April 27, 2004
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	See Reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	No
• Applicant proposed	No
• Reviews	From DMETS 4/21/03
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes, Peds
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	December 2, 1999
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• -Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	4/27/04
❖ Clinical review(s) <i>(indicate date for each review)</i>	2/12/03; 10/15/03; 2/20/04
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	NN
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	10/15/03
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A – Deferred
❖ Statistical review(s) <i>(indicate date for each review)</i>	10/29/03
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	3/1/04; 10/7/03
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	NN
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	AC 7/17/03
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	6/23/03; 8/01/03
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	6/23/03
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	6/23/03
❖ Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	NN
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested – some have been completed.
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	6/11/03
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	NA
❖ CAC/ECAC report	NA

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/s/

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Jena Weber

4/28/04 09:08:39 AM

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\*\*\* TX REPORT \*\*\*  
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ST. TIME 04/27 17:20  
TIME USE 05'49  
PAGES SENT 41  
RESULT OK

### TELEFAX

TO: ANDY

ATTENTION: PAT EGGS

REFERENCE: NDA 21-574

FONTAMET

AD!

FAX#: 201-883-1893

PHONE#: " " 1883

FROM: Jena M. Weber, Project Manager  
Food & Drug Administration  
Division of Metabolic & Endocrine Drug Products, HFD-510  
5600 Fishers Lane, Rockville, MD 20857-1706

Fax: 301-443-9282 Phone: 301-827-6422

DATE: 4/27/04

PAGES: 40



44 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

4-29-04

**Division of Metabolic and Endocrine Drug Products**

**PROJECT MANAGER LABELING REVIEW**

**Application Numbers:** 21-574 Fortamet (metformin HCl) Extended-Release Tablets  
500 mg and 1000 mg.

**Sponsor:** Andrx Labs. Inc.

**Material Reviewed:** Package insert (PI); patient package insert (PPI); carton and container labels.

**Submission Date:** December 17, 2002

**Receipt Date:** December 19, 2002

**Background and Summary Description:** 505(b)(2) application. Indicated as an adjunct to diet and exercise in the treatment of patients with Type 2 Diabetes Mellitus. May be used in monotherapy or in combination with a sulfonylurea or insulin.

**Review:**

**Container Labels:** Acceptable as submitted on February 9, 2004.

500 mg; 60 tablet count, NDC 62022-574-60  
1000 mg; 60 tablet count, NDA 62022-575-60

**Blister Sample Container:** Acceptable as submitted on February 9, 2004.

500 mg; 7 tablet count, NOT FOR SALE, NDA 62022-574-99  
1000 mg; 7 tablet count, NOT FOR SALE, NDC 62022-575-99

**Carton:** Acceptable as submitted on February 9, 2004.

500 mg; 60 tablet count; NDC 62022-574-60  
1000 mg; 1000 mg; 60 tablet count, NDA 62022-575-60

**Package Insert and Patient Package Insert (Patient Information):** Acceptable as submitted on April 27, 2004.

**Conclusions:** Issue approval (AP) letter; request FPL.

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/s/

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Jena Weber  
4/29/04 11:04:06 AM  
CSO

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

3-22-04

2 Page(s) Withheld



       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

3-2-04

NDA 21-574

Andrx Laboratories  
Attention: Josephine Cucchiaro, Ph.D.  
VP, Clinical Research and Regulatory Affairs  
411 Hackensack Avenue, 3<sup>rd</sup> Floor  
Hackensack, NJ 07601

Dear Dr. Cucchiaro:

We acknowledge receipt on February 27, 2004, of your February 26, 2004, resubmission to your new drug application for Fortamet™ (metformin HCl) Extended-Release Tablets, 500 mg and 1000 mg.

We consider this a complete, class 1 response to our February 20, 2004, action letter. Therefore, the user fee goal date is **April 27, 2004**.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on April 9, 2002, for the pediatric study requirement for this application.

If you have any questions, please call me at 301-827-6422.

Sincerely,

*{See appended electronic signature page}*

Jena Weber  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jena Weber  
3/2/04 02:33:07 PM

**Galliers, Enid M**

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**From:** Johnson, Steven B  
**Sent:** Friday, February 13, 2004 2:04 PM  
**To:** 'Patricia.Sass@Andrx.com'  
**Cc:** Galliers, Enid M  
**Subject:** CPB Section of Label and Dissolution Recommendation

Ms. Sass,

Attached is the Clinical Pharmacology section of the label for NDA 21-574. In addition, I've also included the dissolution recommendation. If you should have any questions, please feel free to contact me at 301.827.9086 or at johnsonst@cder.fda.gov.

The proposed dissolution medium, pH [ ] 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>	
<b>Medium</b>	
<b>Volume</b>	
<b>Temperature</b>	
<b>Speed</b>	
<b>Specification</b>	500 mg 1000 mg

Regards,

Steven

\*\*\*\*\*

Steven B. Johnson, Pharm.D.  
Senior Clinical Pharmacology and Biopharmaceutics Reviewer  
Division of Metabolic and Endocrine Drug Products  
5600 Fishers Lane  
HFD-870/RM 13B17  
Rockville, MD 20857



N21574 CPB  
ing Comments

9 Page(s) Withheld

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       § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

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Enid Galliers  
2/16/04 04:18:56 PM  
CSO  
Entered on behalf of Steven B. Johnson, Pharm.D.

**From:** "Johnson  
**To:** "Patricia.Sass@Andrx.com" <Patricia.Sass@Andrx.com>  
**cc:** "Galliers  
**Date:** Friday, February 13, 2004 02:03PM  
**Subject:** CPB Section of Label and Dissolution Recommendation

---

Ms. Sass,

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<<...OLE\_Obj...>>

Regards,

Steven

\*\*\*\*\*

Steven B. Johnson, Pharm.D.  
Senior Clinical Pharmacology and Biopharmaceutics Reviewer  
Division of Metabolic and Endocrine Drug Products  
5600 Fishers Lane  
HFD-870/RM 13B17  
Rockville, MD 20857

<<N21574 CPB Labeling Comments.doc>>

Attachments:



**From:** "Galliers"  
**To:** "'Patricia.Sass@andrx.com'" <Patricia.Sass@andrx.com>  
**cc:** "Misbin, Robert I" <MISBINR@cder.fda.gov>, "Sahlroot, Jon T" <SAHLROOTT@cder.fda.gov>, "Johnson"  
**Date:** Friday, February 13, 2004 03:02PM  
**Subject:** Changes to fortamet labeling

---

Dear Ms. Sass:

Due to technical problems with different versions of MS Word, I am not sending a clean copy of the labeling revisions. However, we include revisions marked in red on pages 10-12 of the labeling you submitted on December 19, 2003. In addition, the text and tables regarding the placebo-controlled trial on pages 12 - 15 should be deleted (further described below). Also, a few additional comments which provide acceptable alternatives are enclosed. Finally, the CLINICAL PHARMACOLOGY section should be revised as indicated in the email sent earlier this afternoon by Dr. Steven Johnson.

-Changes should be made to Table 4 and accompanying text marked in red.

-In addition, the following statement under Table 4

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should be removed entirely or revised to state:

*"Results of this study also indicated that neither Fortamet nor immediate release metformin were associated with weight gain or increase in body mass index"*

-Tables 5 and 6 and accompanying text should be removed.

-Q4 in the PPI should be revised to read:

*"Fortamet, as well as other formulations of metformin, lowers the amount of sugar in your blood...etc..."*  
<<fortamet label.TS changes.doc>>

Please submit clean and marked-up versions of the revised package insert and patient package insert as soon as possible. We can accept secure email submissions but you will need to make an official submission also of either paper or electronic labeling.

Regards,

Enid Galliers  
CPMS, DMEDP  
301-827-6429  
Enid.galliers@fda.hhs.gov

Attachments:



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-574

12/31/03

Andrx Laboratories  
Attention: Josephine Cucchiaro, Ph.D.  
VP, Clinical Research and Regulatory Affairs  
411 Hackensack Avenue, 3<sup>rd</sup> Floor  
Hackensack, NJ 07601

Dear Dr. Cucchiaro:

We acknowledge receipt on December 22, 2003, of your December 19, 2003, resubmission to your new drug application for Fortamet™ (metformin HCl) Extended-Release Tablets, 500 mg and 1000 mg.

We consider this a complete, class 1 response to our October 17, 2003, action letter. Therefore, the user fee goal date is **February 22, 2004**.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on April 9, 2002, for the pediatric study requirement for this application.

If you have any questions, please call me at 301-827-6422.

Sincerely,

*{See appended electronic signature page}*

Jena Weber  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jena Weber  
12/31/03 08:49:37 AM

## DSI CONSULT: Request for Clinical Inspections

**Date:** February 12, 2003

**To:** Andrea Slavin, HFD-46

**From:** Jena Weber, Regulatory Project Manager, HFD-510

**Subject:** **Request for Clinical Inspections**  
NDA 21-574  
Andrx Laboratories  
Fortamet (metformin HCl extended-release) Tablets, 500 mg & 1000 mg.

### **Protocol/Site Identification:**

Dr. Robert Misbin requests that any 2 of the 5 sites identified with study 155-302 be inspected. The following protocols/sites essential for approval have been identified for inspection.

<b>Indication</b>	<b>Protocol #</b>	<b>Site (Name and Address)</b>	<b>Number of Subjects</b>
As an adjunct to diet and exercise for the treatment of patients with Type 2 Diabetes Mellitus.	A Double-Blind, Multicenter, Randomized, Parallel Group, Phase III Study Comparing the Tolerability and Safety of 2000 mg and 2500 mg of Metformin XT Q.D. to the Same Dose of Glucophage B.I.D. in Patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM). 155-302	Total of five sites: 002, 003, 010, 014, 015.	

### **Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **August 15, 2003**. We intend to issue an action letter on this application by (action goal date) **October 1, 2003**.

Should you require any additional information, please contact Ms. Jena Weber, at 301-827-6422.

Please note that all sections of this application may be accessed through the Electronic Document Room (EDR).

Concurrence: Robert I. Misbin, M.D., Medical Reviewer, HFD-510  
David G. Orloff, M.D., Division Director, HFD-510

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/s/

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Robert Misbin  
2/14/03 02:49:05 PM

# REQUEST FOR CONSULTATION

TO (Division/Office): DDMAC, Attention: Laura Pincock, PharmD/Jeanine Best, MSN, HFD-42

FROM: DMEDP, Jena Weber, HFD-510

1/2/04

IND NO. N/A

NDA NO. 21-574

TYPE OF DOCUMENT PI/PPI

DATE OF DOCUMENT: 12/19/03

NAME OF DRUG: Fortamet (metformin HCl) E-R Tablets

PRIORITY CONSIDERATION: NO

CLASSIFICATION OF DRUG: Oral Hypoglycemic agent

DESIRED COMPLETION DATE: 2/1/04

NAME OF FIRM: Andrx

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input checked="" type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

#### STATISTICAL EVALUATION BRANCH

#### STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- DISSOLUTION  
 BIOAVAILABILITY STUDIES  
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE  
 PROTOCOL-BIOPHARMACEUTICS  
 IN-VIVO WAIVER REQUEST

### IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL  
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES  
 CASE REPORTS OF SPECIFIC REACTIONS (List below)  
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  
 SUMMARY OF ADVERSE EXPERIENCE  
 POISON RISK ANALYSIS

### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This submission is in response to our "AE" letter dated 10/17/03. Please review & comment prn on the revised PI and PPI.

NOTE: UFGD is 2/22/04.

SIGNATURE OF REQUESTER Jena Weber, PM via DFS

METHOD OF DELIVERY (Check one): DFS

SIGNATURE OF RECEIVER: Laura Pincocl

SIGNATURE OF DELIVERER

**FORTAMET™ (metformin hydrochloride) Extended-Release Tablets**

**DESCRIPTION**

**MEMORANDUM**

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

**DATE:** October 20, 2003  
**TO:** NDA file 21-574  
**FROM:** Jena Weber, PM  
**SUBJECT:** **Patient Package Insert (PPI) for Fortamet**  
(metformin extended-release tablets)

The sponsor of this NDA (Andrx Labs) was issued an **approvable** letter on October 17, 2003. Outstanding deficiencies are for the 500 mg tablets to demonstrate bioequivalence. Data from an ongoing study to support bioequivalence should be submitted to the Agency by mid-December 2003.

The **approvable** action also contained recommendations for the PI and PPI. However, only comments 1 through 10 for the PPI were referenced in our communication. This should have included all questions and comments 1 through 17. The company was informed of our inadvertent error. The entire document appears as follows:

**PATIENT INFORMATION ABOUT FORTAMET™ (metformin Hydrochloride) extended-release tablets**

**Q1. Why do I need to take FORTAMET™?**

Your doctor has prescribed FORTAMET™ to treat your diabetes, a condition in which blood sugar (blood glucose) is elevated. There are two types of diabetes. FORTAMET™ is indicated for the most common type, know as type 2 diabetes [

]

**Q2. Why is it important to control type 2 diabetes?**

Type 2 diabetes has multiple possible complications, including blindness, kidney failure, and circulatory and heart problems. [

]

5 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

**Q17. Where can I get more information about FORTAMET™?**

This leaflet is a summary of the most important information about FORTAMET™. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type 2 diabetes as well as FORTAMET™ and its side effects.

Distributed by Andrx Laboratories, Inc.  
Weston, Florida 33331

[ ]

Additional comments may be offered before the Agency issues an approval letter.

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/s/

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Jena Weber  
10/20/03 08:22:32 AM  
CSO

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center For Drug Evaluation and Research

**DATE:** October 17, 2003

**FROM:** David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products

**TO:** NDA 21-574  
Fortamet (metformin extended release) Tablets  
Andrx Labs, Inc.  
Treatment of type 2 DM (reference Glucophage)

**SUBJECT:** NDA review issues and recommended action

**Background**

This is a 505(b)(2) application for an extended-release metformin product referencing the approved product Glucophage (immediate-release metformin).

**Clinical Safety and Efficacy**

One study was conducted to establish non-inferiority of Fortamet once daily to Glucophage (immediate-release) twice daily for glycemic control in type 2 DM. After a six-week titration period, doses of both drugs were held constant for the remaining 20 weeks of the trial. The mean difference in HbA1c change from baseline between the two treatment groups was 0.27 percentage units favoring Glucophage (more effective). The upper bound of the 95% CI for the difference was 0.365 (less than the criterion 0.4), so that the statistical and clinical non-inferiority criterion was met. There were no previously unrecognized metformin-associated safety or tolerability issues identified in the clinical program.

**Biopharmaceutics**

Dosage form equivalence between the proposed 500 mg and 1000 mg doses has not been established. To the extent that adequate Biopharmaceutics information has been provided for the 1000 mg tablet, it may be approved. There is insufficient overall biopharm information for the 500 mg tablet and it cannot be approved at this time. The utility of the product depends significantly upon the existence of the 500 mg tablet.

**Labeling**

Labeling comments are being conveyed with the action letter.

**Pharmacology/Toxicology**

No issues.

**Chemistry/ Microbiology**

ONDC recommends approval with no phase 4 commitments.

**DSI/Data Integrity**

Several sites for the pivotal clinical trial were audited. There were no significant deficiencies. Data from all sites were acceptable for review.

NDA # 21-574  
Drug: Fortamet (metformin extended release)  
Proposal: type 2 DM  
10/17/03

**Financial disclosure**

The financial disclosure information is in order as reviewed by Dr. Misbin.

**ODS/nomenclature**

The tradename Fortamet was acceptable to DMETS.

**Recommendation**

Approvable, pending further Biopharmaceutics data on the 500 mg tablet, and on final agreement on labeling.

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/s/

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David Orloff  
10/17/03 01:08:57 PM  
MEDICAL OFFICER

**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**(DMETS; HFD-420)**

**DATE RECEIVED:** 02/03/03

**DUE DATE:** 04/18/03

**ODS CONSULT #:** 02-0176-1

**TO:** David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

**THROUGH:** Jena Weber  
Project Manager  
HFD-510

**PRODUCT NAME:**  
  
**Fortamet**  
(Metformin Extended-Release Tablets)  
500 mg and 1000 mg

**NDA:** 21-574

**MANUFACTURER:**  
  
Andrx Labs.

**SAFETY EVALUATOR:** Alina R. Mahmud, R.Ph.

**SUMMARY:** In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), DMETS reviewed the proposed blister pack and container labels, carton and patient package insert labeling of Fortamet for possible interventions that may help minimize medication errors.

**DMETS RECOMMENDATION:** DMETS recommends the implementation of the proposed labeling revisions outlined in section II of this review in order to minimize the potential for medication errors.

*Sent to  
company  
4/30/03*

*/S/*

*/S/*

Carol Holquist, R.Ph.  
Deputy Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**Label and Labeling Review**

**DATE OF REVIEW:** April 15, 2003

**NDA:** 21-574

**NAME OF DRUG:** **Fortamet**  
(Metformin Extended-Release Tablets)  
500 mg and 1000 mg

**NDA HOLDER:** Andrx Labs.

**I. INTRODUCTION**

This consult is in response to a February 3, 2003 request by the Division of Metabolic and Endocrine Drug Products to review the blister pack labels, container labels, carton and patient package insert labeling for possible interventions in minimizing medication errors.

The proprietary name Fortamet was previously reviewed by DMETS on October 22, 2002 and was found acceptable. Container labels and carton labeling were not reviewed at that time.

**PRODUCT INFORMATION**

Fortamet Extended-Release Tablets contain metformin hydrochloride and is indicated as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed on diet and exercise alone. Fortamet can be used concomitantly with a sulfonylurea or insulin when diet, exercise, or a sulfonylurea or insulin, alone, does not result in adequate glycemic control. Fortamet is indicated in patients 17 years of age and older. Fortamet should generally be given once daily with the evening meal. The recommended starting dose is 1000 mg once daily with the evening meal. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2500 mg once daily with the evening meal. Fortamet will be available as 500 mg and 1000 mg extended-release tablets.

## II. LABELING, PACKAGING AND SAFETY RELATED ISSUES

DMETS has reviewed the blister pack labels, container labels, carton and patient insert labeling of Fortamet and has identified areas of possible improvement, which might minimize potential user error.

### A. GENERAL COMMENT

In general, extended-release tablets should not be broken, crushed, or chewed since it alters the release rate of the active ingredient. The container, carton and insert labeling does not include a statement to this effect. Please include if appropriate.

### B. CONTAINER LABELS (60 tablets)

1. We note the net quantity appears more prominently than the product strength. Therefore, decrease the prominence of the net quantity statement.
2. We note that the color of the proprietary name appears differently on labels and labeling dependent upon the product strength. For example, "FORTA" is highlighted in — whereas "MET" is highlighted in — for the 500 mg strength. This presentation highlights the "FORTA" part of the name which conveys a meaning of strength. Please revise so that the full name appears in one color rather than two. Additionally, the product strengths should be differentiated in color rather than the proprietary name.
3. Increase the prominence of the established name so it appears at least half the size of the proprietary name as per 21 CFR 201.10(g)(2).
4. Revise the "Each tablet contains" statement on the side panel to "Each extended-release tablet contains..".
5. Since this product has a different dosing regimen, we encourage a more explicit dosage statement on the side panel. Revise as follows:

USUAL DOSAGE: 1500 mg to 2500 mg once daily with an evening meal.  
See package insert.

### III. RECOMMENDATION

DMETS recommends the implementation of the labeling revisions outlined in section II of this review in order to prevent the potential for medication errors.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, Project Manager, at 301-827-3242.

/s/

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Alina Mahmud, RPh  
Team Leader  
Division of Medication Error and Technical Support

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/s/

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Alina Mahmud  
4/21/03 10:37:36 AM  
PHARMACIST

Carol Holquist  
4/21/03 11:16:04 AM  
PHARMACIST

Jerry Phillips  
4/21/03 11:19:19 AM  
DIRECTOR



Food and Drug Administration  
Division of Metabolic and Endocrine  
Drug Products, HFD-510  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

DATE:

9/24/03

To:

Dr. Farina

From:

Dr. Jim Wei

Company:

Andrx Labs

Division of Metabolic and Endocrine Drug  
Products

Fax number:

201-883-1893

Fax number: (301) 443-9282

Phone number:

Phone number:

Subject:

Data request for Fortamet

Total no. of pages including cover:

2

Comments:

Document to be mailed:

 YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.

Three additional requests from Dr Jim Wei:

- 1) On Page 168 of Volume 24, you have Table 4.1.28 for  $f_2$  values for dissolution testing for revised composition/process. However, there is no raw data for dissolution tests. In order for us to evaluate, we need raw data of these dissolution profiles.
- 2) In order to set up appropriate dissolution specifications, we need to evaluate dissolution profiles for lots used in pivotal clinical trials and commercial production lots. We did not see any data for commercial lots. Please provide these raw data from dissolution testing.
- 2) Based on our guidance for "Extended release oral dosage forms: development, evaluation, and application of In Vitro/In Vivo correlation", your proposed dissolution specs at 2<sup>nd</sup> time point (8 hr) is wider than what we can accept  You proposed  window for 8 hours, would you please to narrow your specs for 8 hour time point. The 3<sup>rd</sup> time point, 16 hours is too loose. Please set the 3<sup>rd</sup> time point earlier, like 12 hour. Please consider this suggestion, re-propose your specs and send us these specs with your reasons back to us.

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       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

7-16-03

5 Page(s) Withheld



       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling



NDA 21-574

**DISCIPLINE REVIEW LETTER**

Andrx Laboratories  
Attention: Nicholas Farina, Ph.D.  
Vice President, Regulatory Affairs  
401 Hackensack Avenue  
Hackensack, NJ 07601

4/30/03

Dear Dr. Farina:

Please refer to your December 17, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortamet (metformin extended-release tablets) 500 mg and 1000 mg.

The Division of Medication Errors and Technical Support (DMETS) has completed their review of your proposed blister pack, carton and container labels, and have identified areas of possible improvement, which might minimize potential user error. Please address these in writing to your NDA file.

**LABELING, PACKAGING AND SAFETY RELATED ISSUES**

**A. GENERAL COMMENT**

In general, extended-release tablets should not be broken, crushed, or chewed since it alters the release rate of the active ingredient. The container, carton and insert labeling does not include a statement to this effect. Please include if appropriate.

**B. CONTAINER LABELS (60 tablets)**

1. We note the net quantity appears more prominently than the product strength. Therefore, decrease the prominence of the net quantity statement.
2. We note that the color of the proprietary name appears differently on labels and labeling dependent upon the product strength. For example, "FORTA" is highlighted in — whereas "MET" is highlighted in — for the 500 mg strength. This presentation highlights the "FORTA" part of the name which conveys a meaning of strength. Please revise so that the full name appears in one color rather than two. Additionally, the product strengths should be differentiated in color rather than the proprietary name.

3. You should increase the prominence of the established name so it appears at least half the size of the proprietary name as per 21 CFR 201.10(g)(2).
4. Please revise the "Each tablet contains" statement on the side panel to, "Each extended- release tablet contains. . . .".
5. Since this product has a different dosing regimen, we encourage a more explicit dosage statement on the side panel. Please revise to read:

USUAL DOSAGE: 1500 mg to 2500 mg once daily with an evening meal.  
See package insert.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
4/30/03 02:59:58 PM



**ADDENDUM - NO FILING REVIEW ISSUES IDENTIFIED**

NDA 21-574

3-7-03

Andrx Labs, Inc.  
Attention: Nicholas J. Farina, Ph.D.  
Vice President, Regulatory Affairs  
401 Hackensack Avenue, 9<sup>th</sup> Floor  
Hanensack, NJ 07601

Dear Dr. Farina:

Please refer to your December 17, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortamet (metformin extended-release) Tablets, 500 mg and 1000 mg.

We also refer to our February 13, 2003, letter specifying that this application will be filed on February 17, 2003, and requesting additional information. Also, please address the following:

We note a lack of dosage equivalence between the 500 mg and 1000 mg tablets. Please provide additional information about which tablets were used at the various dose levels in the clinical trials. That is, was 1500 mg given as 1000 mg + 500 mg or as 3 x 500mg?

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call me at (301) 827-6422.

Sincerely,

*{See appended electronic signature page}*

Jena Weber  
Regulatory Health Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jena Weber  
3/7/03 02:28:21 PM



**NO FILING REVIEW ISSUES IDENTIFIED**

NDA 21-574

2/13/03

Andrx Labs, Inc.  
Attention: Nicholas J. Farina, Ph.D.  
Vice President, Regulatory Affairs  
401 Hackensack Avenue, 9<sup>th</sup> Floor  
Hackensack, NJ 07601

Dear Dr. Farina:

Please refer to your December 17, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fortamet (metformin extended-release) Tablets, 500 mg and 1000 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b)(2) of the Act on February 17, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. However, patients in study 302 received 2000 mg or 2500 mg of metformin as a new medication; the mean HbA1c level did not decrease. Please submit HbA1c data (baseline, endpoint, and change for each patient and mean  $\pm$  for each group), for the 14 treatment-naïve patients randomized to Metformin E-R, and the 11 treatment-naïve patients randomized to Glucophage.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson, R.Ph.  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jena Weber  
2/13/03 08:46:18 AM  
Jena Weber for Kati Johnson

## NDA REGULATORY FILING REVIEW

NDA 21-574 Fortamet (metformin HCL extended-release) Tablets, 500 mg and 1000 mg.

Applicant: Andrx

Date of Application: December 17, 2002

Date of Receipt: December 19, 2002

Date of Filing Meeting: February 11, 2003

Filing Date: February 17, 2003

AE's issued: February 20, 2004, and October 17, 2003.

Indication requested: As an adjunct to diet and exercise in the treatment of patients with Type 2 Diabetes Mellitus. To be used in monotherapy or in combination with a sulfonylurea or insulin.

Type of Application: Full NDA  Supplement \_\_\_\_\_  
(b)(1) \_\_\_\_\_ (b)(2)   
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classifications: S  P \_\_\_\_\_

Resubmission after a withdrawal or refuse to file: N/A

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.) N/A

User Fee Status: Paid  Waived (e.g., small business, public health): NO

Exempt (orphan, government): NO

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee ID# 4435

Clinical data? YES

Date clock started after UN: N/A

User Fee Goal date: April 27, 2004

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES  
**If foreign applicant, the U.S. Agent must countersign or submit a separate certification.**
- Submission complete as required under 21 CFR 314.50? YES
- If no, explain:
- If electronic NDA, does it follow the Guidance? YES

- Patent information included with authorized signature? YES
- Exclusivity requested? YES; 3 years
- Correctly worded Debarment Certification included with authorized signature? YES  
**If foreign applicant, the U.S. Agent must countersign or submit a separate certification.**

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that \_\_\_\_\_ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix \_\_\_\_." Applicant may not use wording such as, "To the best of my knowledge, ...."

- Financial Disclosure included with authorized signature? YES  
 (Forms 3454 and/or 3455)  
**If foreign applicant, the U.S. Agent must countersign or submit a separate certification.**
- Pediatric Rule appears to be addressed for all indications? NO
- Pediatric assessment of all ages? NO  
 (If multiple indications, answer for each indication.)  
 If NO, for what ages was a waiver requested?  
 For what ages was a deferral requested? Deferral granted 4/9/02 for pediatric patients aged 10 -16.
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

**Refer to 21 CFR 314.101(d) for Filing Requirements**

PDUFA and Action Goal dates correct in COMIS? YES  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES

List referenced IND numbers: 55,962

End-of-Phase 2 Meeting? Yes; 12/2/99  
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? NO  
 If yes, distribute minutes before filing meeting.

**Project Management**

Copy of the labeling (PI) sent to DDMAC? YES  
Trade name and labeling (PI) sent to ODS? (DMETS) YES  
PI & PPI to OPSS? YES  
Advisory Committee Meeting needed? NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NN

**Chemistry**

- Did sponsor request categorical exclusion for environmental assessment? YES  
If no, did sponsor submit a complete environmental assessment? YES
- EA consulted to Nancy Sager (HFD-357)? NO
- Establishment Evaluation Request (EER) package submitted? YES
- Parenteral Applications Consulted to Sterile Products (HFD-805)? NN

**505(b)(2)**

Describe the change from the listed drug(s) provided for in this (b)(2) application.

This application provides for a new formulation of metformin HCl extended-release 500 mg and 1000 mg tablets. The listed drug, Glucophage XR® (metformin HCl extended-release tablets), is approved as 500 mg and 750 mg tablets. The Andrx 500 mg tablet is physically smaller than the 500 mg tablets from BMS.

Name of listed drug(s) and NDA 20-357; Glucophage (metformin HCl) Tablets.

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?

Yes \_\_\_ No  \_\_\_

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

Yes \_\_\_ No  \_\_\_

If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

Yes \_\_\_ No  \_\_\_

If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following does the application contain? Note that a patent certification must contain an authorized signature.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

\_\_\_ 21 CFR 314.50(i)(1)(ii): No relevant patents.

\_\_\_ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

\_\_\_ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? YES
- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity? YES
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? YES

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES

ATTACHMENT  
FILING MEETING MINUTES

DATE: February 11, 2003.

ATTENDEES: Dr. Misbin, Sahlroot, Ysern, Wei, Xiao, Ms. Weber.

ASSIGNED REVIEWERS:

**Discipline**

**Reviewer**

Medical:

David Orloff, M.D.

Secondary Medical:

Robert Misbin, M.D.

Statistical:

Todd Sahlroot, Ph.D.

Pharmacology:

Shen Xiao, Ph.D.

Statistical Pharmacology:

NN

Chemist:

Xavier Ysern, Ph.D.

Environmental Assessment (if needed):

Biopharmaceutical:

Jim Wei, M.D., Ph.D.

Microbiology, sterility:

NN

Microbiology, clinical (for antimicrobial products only):

NN

DSI:

Project Manager:

Jena Weber

Other Consults:

ODS – Sammie Beam

OPASS – Jeanine Best

Is the application affected by the application integrity policy (AIP) NO

Per reviewers, all parts in English, or English translation? YES

CLINICAL – File

• Clinical site inspection needed: NO

MICROBIOLOGY CLINICAL – N/A

STATISTICAL – File

BIOPHARMACEUTICS – File

• Biopharm. inspection Needed: NO

PHARMACOLOGY – File

CHEMISTRY – File

• Establishment ready for inspection? YES

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

Jena M. Weber  
Project Manager, HFD-510

*Appears This Way  
On Original*

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/s/

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Jena Weber  
4/28/04 09:38:41 AM  
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420, Attention: Sammie Beam, R.Ph.			FROM: Division of Metabolic & Endocrine Drug Products, HFD 510 Attention: Jena Weber, Project Manager		
TE: 2/3/03	IND NO. N/A	NDA NO. 21-574	TYPE OF DOCUMENT: Original NDA application, labeling	DATE OF DOCUMENT: 12/17/03 & 2/3/03.	
NAME OF DRUG: Metformin Extended Release Tablets		PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: Anti-diabetic oral agent.		DESIRED COMPLETION DATE: 7/1/03
NAME OF FIRM: Andrx Labs.					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>					
DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Request review & comment on labels & labeling (sent via e-mail Acrobat) submitted by company.					
<b>UFGD is 10/19/03.</b>					
SIGNATURE OF REQUESTER: Jena Weber (x76422)			METHOD OF DELIVERY: DFS		
SIGNATURE OF RECEIVER: Sammie Beam			SIGNATURE OF DELIVERER		

**REQUEST FOR CONSULTATION**

TO (Division/Office): OPSS  
Attention : Leslie Stephens, Project Manager HFD-410

FROM: Division of Metabolic and Endocrine Drug Products, HFD-510  
Jena Weber, Project Manager

TE 1/23/03	IND NO. N/A	NDA NO. 21-574	TYPE OF DOCUMENT: Original NDA; PI & PPI	DATE OF DOCUMENT: 12/17/02
NAME OF DRUG: Fortamet (metformin HCl extended release) Tablets		PRIORITY CONSIDERATION: Standard Review clock (10 mo)	CLASSIFICATION OF DRUG: Oral Hypoglycemic agent	DESIRED COMPLETION DATE: 08/30/03

NAME OF FIRM: Andrx

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

**IV. DRUG EXPERIENCE**

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Please review and comment on the sponsor's proposed PPI and PI. See attached LBL; EDR copy also available.

SIGNATURE OF REQUESTER: Jena Weber, PM

METHOD OF DELIVERY (Check one): DFS

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

*DFS to  
RST/hrs thru  
D 01/23/03*

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/s/

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Leslie Stephens  
1/31/03 12:24:10 PM

**Weber, Jena M**

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**From:** Lechter, Karen J  
**Sent:** Thursday, January 09, 2003 8:09 AM  
**Subject:** RE: NDA 21-574

Thanks for the heads up. This should go to Leslie Stephens, who is our project manager. It might go to me, but it might instead go to Jeanine Best. If you have the consult electronically, you can send it to CDER OPASS CONSULTS. However, please contact Leslie to find out where to send the materials. Her phone number is x73235.

Thanks  
Karen

-----Original Message-----

**From:** Weber, Jena M  
**Sent:** Tuesday, January 07, 2003 1:04 PM  
**To:** Lechter, Karen J  
**Subject:** NDA 21-574

OPSS  
MED-410

Karen,

I have received a 505b2 from Andrx for Fortamet (metformin HCl extended-release) tablets. Along w the proposed LBL, it has a PPI that follows the PI. Should you review this, and if so, who should I send the consult to?  
Thanks,  
Jena

3 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-574

12|27|02

Andrx Labs, Inc.  
Attention: Nicholas J. Farina, Ph.D.  
Vice President, Regulatory Affairs  
401 Hacksensack Avenue, 9<sup>th</sup> Floor  
Hackensack, NJ 07601

Dear Dr. Farina:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Fortamet (metformin extended-release) Tablets, 500 mg and 1000 mg.
Review Priority Classification:	Standard
Date of Application:	December 17, 2002
Date of Receipt:	December 19, 2002
Our Reference Number:	NDA 21-574

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 19, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Products, HFD-510  
Attention: Division Document Room, 8B45  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-574

Page 2

If you have any questions, please call me at 301-827-6422.

Sincerely,

*{See appended electronic signature page}*

Jena Weber  
Regulatory Health Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jena Weber

12/27/02 07:40:26 AM

# USER FEE COVER SHEET

**See Instructions on Reverse Side Before Completing This Form**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdofa/default.htm>

<b>1. APPLICANT'S NAME AND ADDRESS</b>  Andrx Labs, Inc. 401 Hackensack Avenue 9 <sup>th</sup> Floor Hackensack, NJ 07601	<b>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</b> 21-574
<b>2. TELEPHONE NUMBER (Include Area Code)</b>  ( 201 ) 883-1883	<b>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</b> <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <b>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</b> <b>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</b> <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA).
<b>3. PRODUCT NAME</b> Fortamet (metformin hydrochloride) Extended-Release Tablets	<b>6. USER FEE LD. NUMBER</b> 4435

**7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.**

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/18/82 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

**8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?**  YES  NO  
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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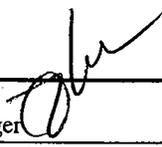
<b>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</b> <i>Michael S. Fawcett</i> <i>Jan A. Daily</i>	<b>TITLE</b> Vice President, Regulatory Affairs Director of R & D Finance	<b>DATE</b> 11/26/12
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Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation ODE II

**FACSIMILE TRANSMITTAL SHEET**

**DATE: November 15, 2002**

<b>To:</b> Nicholas Farina, Ph.D. Vice President, Regulatory Affairs	<b>From:</b> Jena Weber Project Manager 
<b>Company:</b> Andrx Laboratories, Inc.	Division of Metabolic and Endocrine Drug Products, HFD-510
<b>Fax number:</b> 201-883-1893	<b>Fax number:</b> 301-443-9282
<b>Phone number:</b> 610-428-2417	<b>Phone number:</b> 301-827-6422

**Subject:** Reference IND 55,962, submission dated July 2, 2002, serial number 048, request for review of proposed tradenames: [ ], Fortamet, [ ]

**Total no. of pages including cover:** 1

**Comments:** The Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety (ODS), has completed their review of your request for proposed tradenames for your formulation of Metformin Extended-Release Tablets, and have the following comments. The Division of Metabolic and Endocrine Drug Products concurs with these recommendations.

1. DMETS does not recommend the use of the proprietary name, [ ] However, we have no objection to the use of the proprietary name Fortamet.

This decision is considered tentative. This name along with the accompanying labels and labeling must be re-evaluated upon submission of the NDA, and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. When available, the container and carton labels should be submitted for our review and comment.

**Document to be mailed:**             YES             NO

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.

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/s/

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Jena Weber  
11/15/02 10:49:00 AM  
CSO

Jena Weber  
11/15/02 10:52:51 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 55,962

4-9-02

Aura Laboratories, Inc.  
Attention: Nicholas Farina, Ph.D.  
401 Hackensack Avenue, 9<sup>th</sup> Floor  
Hackensack, NJ 07601

Dear Dr. Farina:

Please refer to your submissions dated December 20, 2001, and March 12, 2002, requesting a deferral of pediatric studies for Metformin Extended Release Tablets.

We have reviewed your submission and agree that a deferral of pediatric studies in patients 10 to 16 years of age is justified for Metformin XT in the treatment of patients with type 2 diabetes mellitus.

Accordingly, pediatric studies are deferred for your application under 21 CFR 314.55 until December 31, 2004.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422.

Sincerely

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
4/9/02 04:59:56 PM