

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-748**

**ADMINISTRATIVE**  
**DOCUMENTS/CORRESPONDENCE**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER  
21-748  
NAME OF APPLICANT / NDA HOLDER  
Hiovail Laboratories, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)  
GLUMETZA™ (metformin hydrochloride) Extended Release Tablets

ACTIVE INGREDIENT(S) Metformin Hydrochloride	STRENGTH(S) 1000 mg
---	------------------------

DOSAGE FORM  
Extended-release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

*FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.*

*For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.*

**1. GENERAL**

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
--------------------------------	-------------------------	------------------------------

d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  Yes  No

*For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.*

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

*Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:*

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

4/8/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

John Dubeck, Esq.

Address

1001 G Street, N.W., Ste 500W

City/State

Washington, D.C.

ZIP Code

20001

Telephone Number

(202) 434-4125

FAX Number (if available)

(202) 434-4654

E-Mail Address (if available)

dubeck@khlaw.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration  
CDER (HFT)-007  
5600 Fishers Lane  
Rockville, MD 20857

*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.*

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

21-748

NAME OF APPLICANT / NDA HOLDER

Biovail Laboratories, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

GLUMETZA (metformin hydrochloride) Extended Release Tablets

ACTIVE INGREDIENT(S)

Metformin Hydrochloride

STRENGTH(S)

500 mg

DOSAGE FORM

Extended release tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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**1. GENERAL**

a. United States Patent Number

6,723,340

b. Issue Date of Patent

01/20/2004

c. Expiration Date of Patent

10/25/2021

d. Name of Patent Owner

DepoMed, Inc.

Address (of Patent Owner)

1360 O'Brien Drive

Attn: Edward Mondell

City/State

Menlo Park, California

ZIP Code

94025

FAX Number (if available)

(650) 462-9993

Telephone Number

(650) 462-5000

E-Mail Address (if available)

emandell@depomedinc.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.96 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in T. e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

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2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

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2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

*Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:*

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**B. Declaration Certification**

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

4/30/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(e)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name John Dubeck, Esq.	
Address 1001 G Street, N.W., Ste 500 W	City/State Washington, D.C.
ZIP Code 20001	Telephone Number (202) 434 4125
FAX Number (if available) (202) 434-4654	E-Mail Address (if available) jdubuck@rlhlaw.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*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.*



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 the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request? No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

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

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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            Metformin HCl extended-release tablets

NDA 21-574            Metformin HCl extended-release tablets

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).

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) 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 8.

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.

(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 8:

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(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:

**Study 81-0003**  
**Study 81-0014**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /✓/

If you have answered "yes" for one or more investigations,



Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

**Yes for Investigation 81-003                    IND 57,548**  
**Yes for Investigation 81-0014                IND 57,548**

(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 _____	!	NO /___/ Explain _____	
	!		
Investigation #2	!		
YES /___/ Explain _____	!	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: \_\_\_\_\_

Signature  
Title:

Date

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
David Orloff

6/29/05 03:36:14 PM

## **1.14 Claimed Exclusivity**

Pursuant to 21 CFR §314.108 (b)(4) Biovail Laboratories Incorporated is claiming Hatch-Waxman exclusivity for a period of three years after the approval date of this application, NDA 21-748. This application contains reports of new clinical investigations (other than bioavailability studies), which to the best of the applicant's knowledge meet the definition of "new clinical investigations" set forth in 21 CFR §314.108 (a), are essential to its approval, and were conducted or sponsored by Biovail Laboratories Incorporated.

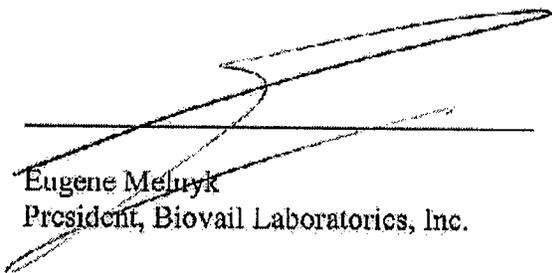


**GLUMETZA™ (metformin hydrochloride)**  
**Extended-Release Tablets, 500 mg and 1000 mg**

**DEBARMENT CERTIFICATION**

New Drug Application

Biovail Laboratories, Inc. hereby certifies that it 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 this application.



Eugene Melnyk  
President, Biovail Laboratories, Inc.

April 15/04  
Date

Biovail Laboratories Inc.  
Chelston Park, Building 2  
Collymore Rock, St. Michael,  
BH1, Barbados, W.I.

# PEDIATRIC PAGE

NDA 21-748

Stamp Date: April 6, 2005 PDUFA Goal Date: June 6, 2005

HFD-510 Trade and generic names/dosage form: Glumetza (metformin HCL extended-release) Tablets

Applicant: Biovail Therapeutic Class: 5S

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A  
(Each indication covered by this application must have pediatric studies: Completed, Deferred, and/or Waived.)

Number of indications for this application(s): \_\_\_\_\_

Indication #1: \_\_\_\_\_

Is this an orphan indication? No.

Is there a full waiver for this indication (check one)? No.

Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

## Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

## Section B: Partially Waived Studies

Age/weight range being partially waived: For children less than 10 years of age.

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred: Ages 10 to 17 years of age.

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due: December 31, 2007

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-748  
HFD-960/ Rosemary Addy or Grace Carmouze  
(revised 2-28-2005)

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Jena Weber  
6/15/05 11:04:00 AM

**Division of Metabolic and Endocrine Drug Products**

**PROJECT MANAGER LABELING REVIEW**

**NDA Number:** 21-748 Glumetza™ (metformin hydrochloride extended-release) tablets, 500 mg and 1000 mg.

**Sponsor:** Biovail Laboratories, Inc.

**NDA Submission Date:** April 27, 2004

**Receipt Date:** April 27, 2004

**Material Reviewed:**

Final draft PI and PPI labeling submitted on June 1, 2005.  
Carton and container labels submitted on February 15, 2005.

**Background and Summary Description:** GLUMETZA (metformin hydrochloride) extended release tablets, as monotherapy, is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients (18 years and older) with type 2 diabetes. GLUMETZA may be used concomitantly with a sulfonylurea or insulin to improve glycemic control in adults.

**Review:**

**Carton and Container Labels:**

500 mg bottles of 30	1000 mg bottles of 30
500 mg bottles of 100	1000 mg bottles of 90
500 mg bottles of 500	1000 mg bottles of 500
	1000 mg bottles of 1000

**Labeling is acceptable; changes made to according to recommendations specified in DMETS review.**

**Patient Package Insert: Labeling is acceptable as submitted on June 1, 2005. Changes made to according to recommendations specified in DSRCs review. No other changes noted.**

**Package Insert: Acceptable, as submitted on June 1, 2005. No other changes noted.**

**Conclusion:** An approval (AP) letter should be issued; request FPL for PI and PPI.

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/s/

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Jena Weber  
6/16/05 01:43:55 PM  
CSO



NDA 21-748

**DISCIPLINE REVIEW LETTER**

Keller and Heckman  
Attention: John B. Dubeck  
Agent for Biovail Laboratories Incorporated  
1001 G Street, N.W., Suite 500-W  
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your April 27, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glumetza™ (metformin HCl extended-release tablets), 500 mg and 1000 mg.

We also refer to your submission dated April 6, 2005.

The Division of Surveillance, Research, and Communication Support (DSRCS) has completed their review of the proposed patient labeling for Glumetza. We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information.

These revisions are based on draft labeling submitted on April 27, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

**PATIENT INFORMATION GLUMETZA**

*[Comment: Add the phonetic Spelling.]*

**(metformin hydrochloride) extended-release tablets**

Read the Patient Information that comes with GLUMETZA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of

**What is the most important information I should know about GLUMETZA? *[Comment: This section should be included when there is important risk information for the patient and there is a Boxed or Bolded Warning in the PI.]***

**GLUMETZA can cause a rare, but serious condition, called lactic acidosis (a buildup of an acid in the blood) that can cause death.** Lactic acidosis is a medical emergency and must be treated in the hospital. **Stop taking GLUMETZA and call your doctor right away if you get the following symptoms of lactic acidosis.**

- You feel very weak or tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing.
- You have stomach pain with nausea and vomiting, or diarrhea.
- You feel cold, especially in your arms and legs.
- You feel dizzy or lightheaded.
- You have a slow or irregular heartbeat.
- Your medical condition suddenly changes.

**You have a higher chance for getting lactic acidosis with GLUMETZA if you:**

- have kidney or liver problems
- have congestive heart failure that requires treatment with medicines
- drink a lot of alcohol (very often or short-term “binge” drinking)
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and don't drink enough fluids.
- have certain x-ray tests with injectable dye used
- have surgery
- have a heart attack, severe infection, or a stroke
- are 80 years of age or older and have not had your kidney function tested

#### **What is GLUMETZA?**

*[Comment: This section should be consistent with the INDICATION section of the PI. Information on diabetes should be moved to the end of the leaflet or provided as a separate educational sheet.]*

GLUMETZA is used along with diet and exercise to improve blood sugar control in adults with type 2 diabetes. GLUMETZA may also be used with another anti-diabetes medicine called a sulfonylurea or with insulin to improve blood sugar levels in adults.

GLUMETZA helps control your blood sugar in a number of ways. These include helping your body respond better to the insulin it makes naturally, decreasing the amount of sugar your liver makes, and decreasing the amount of sugar your intestines absorb.

GLUMETZA has not been studied in children under 18 years of age.

### **Who should not take GLUMETZA?**

*[Comment: This section should be consistent with the CONTRAINDICATIONS section of the PI.]*

#### **Do not take GLUMETZA if you:**

- have kidney problems
- have heart failure that is treated with medicines
- have a condition called metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- are allergic to GLUMETZA or to any of its ingredients. See the end of this leaflet for a list of ingredients in GLUMETZA.

### **What should I tell my doctor before taking GLUMETZA?**

#### **Tell your doctor about all of your medical conditions including if you:**

- have kidney problems
- have liver problems
- have heart problems
- drink a lot of alcohol
- **are pregnant or planning to become pregnant.** It is not known if GLUMETZA can harm your unborn baby. Talk to your doctor about the best way to control your blood sugar levels while pregnant.
- **are breastfeeding.** It is not known if GLUMETZA passes into your milk and if it can harm your baby. Talk to your doctor about the best way to feed you baby while taking GLUMETZA.

**Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements.** GLUMETZA and some of your other medicines can interact. You may need to have the dose of GLUMETZA or certain other medicines adjusted. Certain other medicines can affect your blood sugar control.

Know the medicines you take. Keep a list of them with to show to your doctor and pharmacist. Talk to your doctor before you start any new medicine.

### **How should I take GLUMETZA?**

- Take GLUMETZA exactly as prescribed. Your doctor will usually start you on a low dose and increase your dose slowly to control your blood sugar levels. Do not change your dose unless told to do so by your doctor.
- Take GLUMETZA once a day in the evening with food.
- **Swallow GLUMETZA tablets whole. Never crush or chew GLUMETZA tablets.** Tell your doctor if you cannot swallow tablets whole. Your doctor will prescribe a different medicine for you.
- **You may see the GLUMETZA tablet shell in your stool.** You may also see a soft mass of the GLUMETZA inactive ingredients in your stool. Both of these are normal to see in your stool.
- Stay on your exercise and diet program and test your blood sugar regularly while taking GLUMETZA.

- Your doctor should monitor your diabetes and do blood tests on you from time to time to check your kidneys and your liver.
- If you miss a dose of GLUMETZA....  
*[Comment: Insert the following sentence: Resume dosing according to schedule.]*
- If you take too much GLUMETZA or overdose, call your doctor or poison control center right away.
- You may need to stop GLUMETZA for a short time if you:
  - are sick with severe vomiting, diarrhea or fever, or if you drink a much lower amount of liquid than normal
  - plan to have surgery
- are having an x-ray procedure with injection of dye.  
Call your doctor right away for instructions.

#### **What should I avoid while taking GLUMETZA?**

Do not drink a lot of alcoholic drinks while taking GLUMETZA. This means you should not binge drink for short periods, and you should not drink a lot of alcohol on a regular basis. Alcohol can increase your chance of getting lactic acidosis.

#### **What are the side effects of GLUMETZA?**

**GLUMETZA can cause a rare, but serious condition, called lactic acidosis** (a buildup of an acid in the blood) **that can cause death.** See "What is the most important information I should know about GLUMETZA?"

**The most common side effects of GLUMETZA include** diarrhea, nausea, and upset stomach. These side effects usually go away after you take the medicine for a while. Taking your medicine with the evening meal can help reduce these side effects.

GLUMETZA rarely causes low blood sugar (hypoglycemia) by itself. However, low blood sugar can happen if you do not eat enough, if you drink alcohol, or if you take other medicines to lower blood sugar.

Tell your doctor if you have side effects that bother you, last for more than a few weeks, come back after they have gone away, or start later in therapy. You may need a lower dose or need to stop taking GLUMETZA.

These are not all the side effects with GLUMETZA. For more information, ask your doctor or pharmacist.

#### **How should I store GLUMETZA?**

- Store GLUMETZA at room temperature, 59° to 86° F (15° to 30° C).
- **Keep GLUMETZA and all medicines out of the reach of children.**

#### **General information about GLUMETZA**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use GLUMETZA for a condition for which it was not prescribed. Do not give GLUMETZA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about GLUMETZA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about GLUMETZA that is written for health professionals. ***[Comment: If available, add your website and/or toll-free number for additional information.]***

**What are the ingredients in GLUMETZA?**

**Active Ingredient:** 500 mg or 1000 mg of metformin HCL

**Inactive Ingredients:** Each 500 mg tablet contains coloring, hypromellose, magnesium stearate, microcrystalline cellulose and polyethylene oxide. Each 1000 mg tablet contains crospovidone, dibutyl sebacate, ethylcellulose, glyceryl behenate, polyvinyl alcohol, polyvinylpyrrolidone, and silicon dioxide. GLUMETZA 500 and 1000 mg tablets both utilize advanced, polymer-based, oral drug delivery systems, which allow delivery of metformin HCl to the upper GI tract.

**Rx Only**

GLUMETZA is a registered trademark of Biovail Laboratories Incorporated.

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 Health 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  
5/3/05 02:18:33 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-748

Keller and Heckman  
Attention: John Dubeck  
Agent for Biovail Laboratories Incorporated  
1001 G. Street, N.W., Suite 500 West  
Washington, DC 20001

Dear Mr. Dubeck:

We acknowledge receipt on April 7, 2005, of your April 6, 2005, resubmission to your new drug application for Glumetza™ (metformin hydrochloride extended-release tablets), 500 mg and 1000 mg.

We consider this a complete, class 1 response to our February 25, 2005, action letter. Therefore, the user fee goal date is **June 7, 2005**.

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 note that you have not fulfilled the requirement. We acknowledge receipt of your request for waiver and deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred 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

4/25/05 10:43:35 AM



A

6 Page(s) Withheld

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

     § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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/s/

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Jeanine Best

5/5/05 03:34:01 PM

**Weber, Jena M**

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**From:** Weber, Jena M  
**Sent:** Friday, February 25, 2005 9:43 AM  
**To:** 'Jack Weet'  
**Subject:** RE: Dissolution specs

**Importance:** High

Jack,

See biopharm's comment. Please commit to accepting this revision as part of your dissolution specs.

Thanks,  
Jena

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the original NDA 21-748 for Glumetza™ in the section of human pharmacokinetics and biopharmaceutics. OCPB has found the application acceptable provided that the sponsor agrees with the Agency's recommendations for dissolution specifications as follows:

Apparatus type USP Apparatus-1 ( —  
Medium  
Speed of rotation ~ RPM Specification 2 hr: — 4 hr: ~ 12 hr: NLT ' —  
Temperature of medium 37oC

# MEMORANDUM

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

**DATE:** February 18, 2005

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

**VIA:** Jena Weber, Regulatory Health Project Manager,  
Division of Metabolic and Endocrine Drug Products  
HFD-510

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCs Review of the Patient Labeling for Glumetza (metformin HCL) extended-release tablets, NDA 21-748

The attached patient labeling represents the revised risk communication materials for Glumetza (metformin HCL) extended-release tablets, NDA 21-748. We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor April 27, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

B

4 Page(s) Withheld

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

     § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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/s/

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Jeanine Best  
2/18/05 07:52:27 AM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
2/18/05 03:04:13 PM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan



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/s/

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Tara Turner  
2/11/05 10:58:17 AM

## Weber, Jena M

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**From:** Culley, Kimberly  
**ti:** Wednesday, February 09, 2005 10:53 AM  
Weber, Jena M; Mahmud, Alina  
**Cc:** Holquist, Carol A; Beam, Sammie  
**Subject:** RE: GLUMETZA NDA 21-748 Response to DMETS letter

Hi Jena,

Thanks for forwarding this.

We note that the sponsor incorporated our recommendations into the revised labels and labeling. Since the sponsor maintained the same color scheme in the latest draft labeling, we have no additional comments.

Thanks so much,  
kim

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

**From:** Weber, Jena M  
**Sent:** Monday, January 31, 2005 8:45 AM  
**To:** Culley, Kimberly; Mahmud, Alina  
**Cc:** Holquist, Carol A  
**Subject:** FW: GLUMETZA NDA 21-748 Response to DMETS letter

See response from company. Comments please.  
Thanks,

.a

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

**From:** Aljuburi, Lina  
**Sent:** Friday, January 21, 2005 12:13 PM  
**To:** Weber, Jena M  
**Subject:** FW: GLUMETZA NDA 21-748 Response to DMETS letter

All yours!  
Let me know if I can help in any way.

Lina

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

**From:** Jack Weet [mailto:Jack.Weet@biovail.com]  
**Sent:** Friday, January 21, 2005 10:58 AM  
**To:** l.aljuburi@fda.hhs.gov  
**Subject:** GLUMETZA NDA 21-748 Response to DMETS letter

Dear Lina,

As indicated in my voicemails to you, Biovail intends to submit the following information to the GLUMETZA NDA this afternoon, in response to the DMETS Discipline Review Letter, dated December 27, 2004.

Here is my letter, and the attachments, for the Glumetza response.

<<20050119DraftDMETS Response.doc>> <<20050120GLUMETZA PI proposed.doc>>  
<<20050120GLUMETZA PI proposed.pdf>> <<3.2.P.7A Container Closure System.pdf>>  
<<Glumetza 1000 mg mock up1.doc>> <<Glumetza 1000 mg mock up1.pdf>> <<Glumetza 500 mg  
mock up1.doc>> <<Glumetza 500 mg mock up1.pdf>> <<3.2.P.7A Container Closure



NDA 21-748

**DISCIPLINE REVIEW LETTER**

Biovail Pharmaceuticals, Inc.  
Attention: Stefan Ochalski  
Director, Regulatory Liaison  
700 Route 202-206 North  
Bridgewater, NJ 08807-0980

Dear Mr. Ochalski:

Please refer to your April 27, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glumetza™ (metformin HCl) extended-release Tablets) 500 mg and 1000 mg.

The Division of Medication Errors and Technical Support (DMETS) has completed their review of your proposed package insert, 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.

**CONTAINER LABEL**

1. Consider the addition of the dosage regimen to the principle display panel. DMETS believes the addition of "once daily" or "once a day" to the principle display panel should help to diminish confusion with the immediate release, 500 mg strength of metformin.

2. Ensure the established name is at least one-half the size of the proprietary name as per 21CFR 201.10(g) (2).

3. Revise the established name to include the formulation (see below).

(metformin hydrochloride extended-release tablets)

4. Assure that child resistant closures are used for bottles intended to be a "unit of use" (e.g. 30 tablet size) to be in accordance with the Poison Prevention Act.

5. DMETS questions why the 1000 mg tablet will be available in a 90 count bottle and the 500 mg in a 100 count bottle.

**INSERT LABELING** (“PRECAUTIONS” section, “Information for the Patients” subsection).

1. Please note that the word “discontinue” is missing from the second sentence of the second paragraph. See “Patients should be advised to ... GLUMETZA immediately and to promptly...”
2. Include in this subsection a statement to explain that the drug product should be administered with food.

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,

*{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  
12/27/04 10:30:29 AM



DUPLICATE



OVERNIGHT COURIER

August 25, 2004

David Orloff, M.D., Director  
Division of Metabolic and Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

RECEIVED

AUG 26 2004

FDR/CDER

SU

ORIG AMENDMENT

FDA Form 356h

**RE: NDA #21-748  
GLUMETZA™ (metformin hydrochloride) Extended Release Tablets  
500 and 1000 mg  
Amendment to Pending New Drug Application-120 Day Safety Update**

Dear Dr. Orloff:

Reference is made to the subject NDA submitted on behalf of Biovail Laboratories Inc. and received by the FDA on April 27, 2004. In accordance with 21 CFR 314.50(d)(5)(vi)(b), Biovail hereby reports there is no additional safety information to amend the NDA at this time.

Sincerely,

*On Behalf of Biovail Laboratories Incorporated*

Stefan Ochalski, MBA  
Director, Regulatory Liaison  
Biovail Technologies Limited

## **1.12 WAIVER REQUEST**

We respectfully request a partial waiver of pediatric studies for children less than 10 years of age and a deferral of pediatric studies for children 10 years and older for GLUMETZA<sup>®</sup> until after approval.

The partial waiver for children less than 10 years of age is being requested for the following reasons:

1. There is a lack of prevalence of type 2 diabetes below the age of 10 years, hence, it does not occur in a substantial number of pediatric patients in this age group.
2. Type 2 diabetes does not have sufficient significance in this age group, because of a lack of prevalence, to constitute a meaningful therapeutic benefit for pediatric subjects in this age group.

Waiver and deferral requests were agreed to by the Division in our pre-NDA meeting held on October 28, 2003.

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> July 2, 2004 <b>DOCUMENT DATE:</b> April 27, 2004	<b>DESIRED COMPLETION DATE:</b> September 12, 2004 <b>PDUFA DATE:</b> February 27, 2005	<b>ODS CONSULT #:</b> 04-0187
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**TO:** David Orloff, MD  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

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

<b>PRODUCT NAME:</b> <b>Glumetza™</b> (Metformin Extended-release Tablets) 500 mg and 1000 mg <b>NDA#:</b> 21-748	<b>NDA SPONSOR:</b> Biovail Corporation
---	---

**SAFETY EVALUATOR:** Kimberly Culley, RPh

**RECOMMENDATIONS:**

- DMETS has no objections to the use of the proprietary name, Glumetza. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated 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 the signature date of this document.
- DMETS recommends implementation of the label and labeling revisions outlined in section III of this review, in order to minimize potential errors with the use of this product.
- DDMAC finds the proprietary name Glumetza acceptable from a promotional perspective.

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

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

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** July 21, 2004

**NDA#** 21-748

**NAME OF DRUG:** Glumetza (Metformin Extended-release Tablets)  
500 mg and 1000 mg

**NDA HOLDER:** Biovail Corporation

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for an assessment of the proprietary name Glumetza in regard to potential name confusion with other proprietary and/or established drug names. Container labels and insert labeling were provided for review and comment.

**PRODUCT INFORMATION**

Glumetza contains metformin in an extended release tablet formulation. Metformin is an oral hyperglycemic used in the management of type 2 diabetes. Metformin improves glucose tolerance in patient with type 2 diabetes, lowering both basal and postprandial plasma glucose. Two strengths will be available, 500 mg and 1000 mg. The recommended initial dose is 1000 mg each evening with food to a maximum of 2000 mg daily. The 500 mg tablets (white, film-coated, and oval shaped) will be debossed with 500 on one side and available in bottles of 30, 100 and 500 tablets. The 1000 mg tablets are white, oval-shaped tablets with 1000 mg printed on one side and available in bottles of 30, 90, 500 and 1000 count.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Glumetza to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Glumetza. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Error Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical skill, professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Glumetza acceptable from a promotional perspective.
2. The Expert Panel identified eight proprietary names that were thought to have the potential for confusion with Glumetza. Additionally, independent review identified two proprietary names (Climara and Alimta) that were thought to have the potential for confusion with Glumetza. These products with the available dosage forms and usual dosage are listed in table 1 (see page 4).

---

<sup>1</sup> MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1>

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel and Independent Review

Product Name	Established name, Dosage Form(s), Strength(s)	Usual adult dose*	Other**
Glumetza	Metformin Extended-release Tablets, 500 mg and 1000 mg	1000 mg each evening with food	
Albenza®	Albendazole Tablets, 200 mg	Weight based: ≥60 kg 400 mg twice a day with meals or < 60 kg 15 mg/kg/day given in divided doses twice a day with meals (maximum total daily dose 800 mg).  Duration of therapy: Hydatid disease: 28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles. Neurocysticercosis: 8 to 30 days	LA
Alimta®	Premixed Disodium Vials for Intravenous Use, 500 mg	500 mg/m <sup>2</sup> intravenously infused over 10 minutes	LA
Climara®	Estradiol Transdermal Patch, 0.025 mg, 0.0375 mg, 0.05 mg, 0.06 mg, 0.075 mg and 1 mg	Apply one patch weekly	LA
Flutamide	Flutamide Capsules, 125 mg	Two capsules three times daily at 8-hour intervals. (total daily dose of 750 mg)	LA
Glucerna®	Enteral nutritional supplement	Enteral nutrition	LA
Glucophage®	Metformin Hydrochloride Tablets, 500 mg, 850 mg and 1000 mg	Start at 500 mg twice/day or 850 mg once/day, given with meals. Increase incrementally at 500 mg/week or 850 mg every 2 weeks, up to a total of 2000 mg/day given in divided doses.	LA
Glucophage® XR	Metformin Hydrochloride, Extended-release Tablets, 500 mg 750 mg	500 mg once/day dosage with increases in increments of 500 mg/week, up to a maximum of 2000 mg once/day with the evening meal.	LA
Glumida (Not marketed in the US)	Acarbose Tablets, 50 mg and 100 mg	100 mg 3 times daily; administered with the first bite of each main meal.	LA
Kaletra®	Lopinavir and Ritonavir Capsules: 133.3 mg/33.3 mg Solution: 80 mg/ 20 mg per milliliter	400/100 mg of lopinavir/ritonavir (3 capsules or 5 mL) twice daily with food	LA
Metra (Discontinued)	Phendimetrazine Tartrate Tablets, 35 mg	17.5 to 35 mg two to three times per day, 1 hour before meals	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

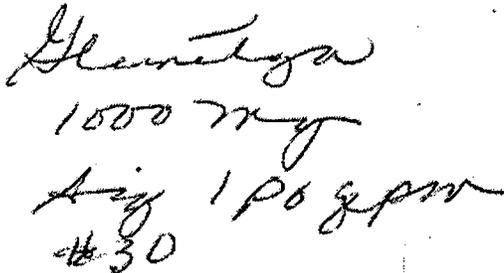
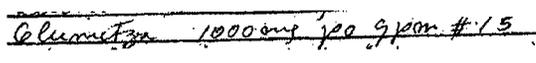
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists that operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Glumetza were captured by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Glumetza with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Glumetza (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p>  <p>Glumetza 1000 mg qd #30</p>	<p>Glumetza 1000 mg Take one every evening with food Dispense number 30</p>
<p><u>Inpatient RX:</u></p>  <p>Glumetza 1000 mg qd #15</p>	

## 2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

### D. SAFETY EVALUATOR RISK ASSESSMENT

#### 1. Look-alike and Sound-alike Names

In reviewing the proprietary name Glumetza, the primary concerns related to look-alike and sound-alike confusion with Albenza, Flutamide, Glucerna, Glucophage, Glucophage XR, Glumida, Kaletra and Metra. Similarly, through independent review, two additional drug names, Alimta and Climara were also determined to have potential for confusion with Glumetza. Upon further review of the names gathered from EPD and independent analysis, the names flutamide, Glumida, Kaletra, and Metra were not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Glumetza. These products also do not share significant overlapping product characteristics such as the product strength, indication for use (except for Glumida), and frequency of administration. In addition, Metra was discontinued from the US market in 1993 and Glumida is not marketed in the United States, therefore the possibility of a practitioner writing for this particular proprietary name is limited.

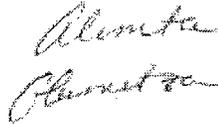
DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, since these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Glumetza.

- a. Albenza may look similar to Glumetza when scripted. Albenza contains albendazole for the treatment of neurocysticercosis (due to active lesions caused by larval forms of the pork tapeworm, *T. solium*) and hydatid disease (of the liver, lung and peritoneum caused by the larval form of the dog tapeworm, *E. granulosus*). Dosing is based on weight, which is as follows: for  $\geq 60$  kilograms dosed at 400 mg twice a day with meals and  $< 60$  kg dosed at 15 mg/kg/day given in divided doses twice a day with meals (maximum total daily dose 800 mg). Treatment for hydatid disease is a twenty-eight day cycle followed by a fourteen-day albendazole-free interval, for a total of three cycles. Treatment for neurocysticercosis continues for eight to 30 days. The primary similarities involve the shared letters of “l” and “za”, which have identical placement and anchor the name visually. In addition, a scripted, capitalized “a” can resemble a “g” (see below).

However, the names can be distinguished by the central “b” and “m” of Albenza and Glumetza, respectively. Furthermore, the “t” of Glumetza may also provide a distinguishing upstroke. The products share two overlapping characteristics that include

the route of administration (oral) and dosage form (tablet). They differ in dosing frequency (twice daily compared with daily), indication (tapeworm treatment compared with diabetes), strength (200 mg compared with 500 mg and 1000 mg), and duration of therapy (less than a month compared with indefinite). The dosing is variable by weight, but the maximum dose of Albenza is 400 mg twice daily; henceforth no possibility to reach the lowest possible dose of Glumetza (500 mg). Since the differing characteristics between the two drug products are significant, confusion between product names should be minimal.

- b. Alimta may look similar to Glumetza when scripted. Alimta contains premetrexed disodium, which is indicated as an adjunct therapy with cisplatin in the treatment of malignant pleural mesothelioma. Alimta is available as a 500 mg vial (powder) for intravenous infusion/injection. Premetrexed is dosed in a 21-day cycle with cisplatin. Dosing is 500 mg/m<sup>2</sup> intravenously infused over 10 minutes. Dosage may be adjusted for hematologic and non-hematologic toxicities. Renal and hepatic impairment may prohibit the use of this product. The visual similarities are primarily due to the shared “l, m, t and a” with similar, if not identical placement. Furthermore, a capitalized and scripted “A” may resemble “G” (see below).



The image shows two lines of handwritten text. The top line is 'Alimta' and the bottom line is 'Glumetza'. The letters 'l', 'm', 't', and 'a' in both words are written in a very similar, cursive style, which could lead to confusion when the words are written together.

However, the presence of the “z” in Glumetza and the letter count (eight compared with six) with resultant name length deviation may help distinguish between the two names. In addition, the products differ in many product characteristics including route of administration (intravenous compared with oral), dosing frequency (one time dose every 21 days compared with daily), dispensing amount (vials count compared with number of tablets), dosage form (injectable compared with tablets), and indication (chemotherapy compared with diabetes). They do share an overlapping strength (500 mg) and one possible dose overlap of 1 gram if a patient has a body surface area of 2 m<sup>2</sup>. However, Alimta is to be used with cisplatin as a dual agent therapy. Henceforth, the products should be written together, which will help to create another visual aid for product distinction. Since the products have different characteristics and the strength of visual similarity is not powerful, DMETS believes the potential for error to be minimal.

- c. Glucerna may look similar to Glumetza when scripted. Glucerna is an enteral nutritional shake for use in patients with abnormal glucose tolerance. Glucerna is also available as meal bars and snack bars. The visual similarities are the result of the shared leading “Glu”, central “e” and ending “a” (see below).

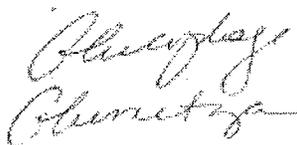


The image shows two lines of handwritten text. The top line is 'Glucerna' and the bottom line is 'Glumetza'. The words share a similar starting 'Glu' and ending 'a', and the central 'e' is also written in a similar style, making them look alike when written together.

However, the “t” upstroke of Glumetza should help to distinguish the names. In addition, Glucerna is an over-the-counter nutritional agent that differs from Glumetza’s prescription-required status. Although prescriptions will generally not be written for this product, the possibility exists for prescriptions to be completed for insurance,

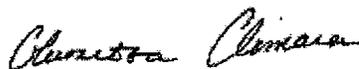
documentation purposes or assisted living facilities. Both products are orally consumed, but they differ in strength (no definable strength for Glucerna compared to the 500 mg and 1000 mg of Glumetza), dosage form (liquid compared to tablet), dispensing amount (number of cans or cases compared with number of tablets), and dosing frequency (variable for Glucerna but usually over one daily compared with once daily). Due to the differences in product characteristics, DMETS believes the potential for confusion is minimal.

- d. Glucophage/Glucophage XR may look similar to Glumetza when scripted. Glucophage contains metformin used in the treatment of type 2 diabetes (as an adjunct to diet and exercise). Metformin is started at 500 mg twice/day or 850 mg once/day, given with meals with subsequent increases of 500 mg/week or 850 mg every 2 weeks, up to a total of 2000 mg/day given in divided doses. Extended-release metformin is started at 500 mg once/day with the evening meal with subsequent increases in increments of 500 mg/week, up to a maximum of 2000 mg once/day with the evening meal. The primary visual similarity results from the shared leading "Glu." In addition, there are the shared downstrokes and letter placement of "g" and "z." This could be compounded by the upstroke of the "h" of Glucophage that can resemble the upstroke of the "t" of Glumetza (see below). However, the placement of these two letters differ that may limit any significance in similarity.



In addition, the names differ in letter count (10 compared with 8), which should create a visual difference in name length. Glucophage may have differing up and downstrokes depending on writing style; the "p" should consistently serve as a differentiating downstroke. As both products share the active ingredient of metformin and indication of diabetes, their similarities are innumerable. For example, they share the key characteristics of route of administration (oral), strengths (500 mg and 1000 mg), dosage form (tablet), and dosing frequency (daily). Furthermore, Glucophage XR and Glumetza share the same extended-release delivery system. Considering the distinctive differences in scripting, DMETS does not believe the written similarity to be convincing to create confusion.

- e. Climara may look similar to Glumetza when scripted. Climara contains estradiol in a transdermal patch for the treatment of menopausal symptoms and the prevention of postmenopausal osteoporosis. The drug product is applied to the skin weekly. The visual similarities result from the resemblance of the leading "Cl" and "Gl" and concluding "ra" and "za" when scripted. This is compounded by the shared central "m" (see below).



However, the "t" of Glumetza should create a defining characteristic on visual appearance. Furthermore, the products share no significant overlapping characteristics as shown by the following: route of administration (topical compared with oral), available strengths (0.025, 0.0375, 0.05, 0.06, 0.075, and 1 mg per hour compared with 500 mg,

1000 mg), and dosing frequency (weekly compared with daily). Due to these product differences, DMETS believes the potential for error is minimal.

### **III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

In the review of the container labels, carton and insert labeling of Glumetza, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement that may minimize potential user error.

#### **A. CONTAINER LABEL**

1. Consider the addition of the dosage regimen to the principle display panel. DMETS believes the addition of “once daily” or “once a day” to the principle display panel should help to diminish confusion with the immediate release, 500 mg strength of metformin.
2. Ensure the established name is at least one-half the size of the proprietary name as per 21CFR 201.10(g) (2).
3. Revise the established name to include the formulation (see below).

(metformin hydrochloride extended-release tablets)

4. Assure that child resistant closures are used for bottles intended to be a “unit of use” (e.g. 30 tablet size) to be in accordance with the Poison Prevention Act.
5. DMETS questions why the 1000 mg tablet will be available in a 90 count bottle and the 500 mg in a 100 count bottle?

#### **B. INSERT LABELING (“PRECAUTIONS” section, “Information for the Patients” subsection)**

1. Please note that the word “discontinue” is missing from the second sentence of the second paragraph. See “Patients should be advised to .... GLUMETZA immediately and to promptly...”
2. Include in this subsection a statement to explain that the drug product should be administered with food.

#### IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Glumetza. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated 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 the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
- C. DDMAC finds the proprietary name Glumetza acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

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Kim Culley, RPh  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

---

Alina Mahmud, RPh  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Appendix A: DMETS Prescription Study Results (Glumetza)

Inpatient	Outpatient	Voice
Glutametz	Glunetza	Glumetza
Glumetza	Gluritga	Glumetsa
Glumetza	Glunetga	Glumetza
Glumetza	Glenitza	Glumetsa
Glumetzra	Glunitga	Glumetza
Glumetza	Glunatza	Glunetsa
GlumieFzen	Glumetza	Glumetza
Columetza	Glunitza	Glumeta
Glumetza	Glunetya	Glumetza
Glumetza	Glunitza	Glumetza
Glumetza	Glumetoza	Clometza
glumetza	Glunetza	Glumetsa
Glumetza	Glunitga	Glumetsa
Glumetza	Glernetiza	
Glumetza	Glunitza	
Glumetazine	Glunatga	
Glumetza	Glunetza	
Olumetza	Glunetga	
	Glumatiga	
	Glunetza	
	Glumetza	

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/s/

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Kimberly Culley  
12/1/04 06:29:33 AM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
12/1/04 07:34:13 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
12/1/04 01:06:33 PM  
DRUG SAFETY OFFICE REVIEWER

**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  
Jena Weber, Project Manager

DATE 7/2/04	IND NO.	NDA NO. 21-748	TYPE OF DOCUMENT: Request for review of tradename – "Glumetza"	DATE OF DOCUMENT: 4/27/04
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NAME OF DRUG: Metformin HCl extended-release tablets	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG: Oral hypoglycemic agent.	DESIRED COMPLETION DATE: 11/15/04
--	----------------------------------	--	-----------------------------------

NAME OF FIRM: Biovail

**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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <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             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

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

Please review and comment on proposed tradename "Glumetza," for this original NDA.  
UFGD = 2/27/05.  
Labeling, carton & containers available via EDR.

SIGNATURE OF REQUESTER: Jena Weber, x76422	METHOD OF DELIVERY: DFS
--	-------------------------

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
-----------------------	------------------------



**FILING COMMUNICATION**

NDA 21-748

Biovail Technologies Ltd.  
Attention: Stefan Ochalski, MBA  
Director-Regulatory Liaison  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Mr. Ochalski:

Please refer to your April 27, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glumetza™ (metformin HCl) Extended Release Tablets, 500 mg and 1000 mg.

We also refer to your submission dated May 7, 2004.

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) of the Act on June 26, 2004, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. 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 Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

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Jena Weber

6/21/04 01:52:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-748

Biovail Technologies Ltd.  
Attention: Stefan Ochalski, MBA  
Director-Regulatory Liaison  
700 Route 202/206 North  
Bridgewater, NJ 08807

Dear Mr. Ochalski:

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

Name of Drug Product:	Glumetza™ (metformin HCl) Extended Release Tablets, 500 mg and 1000 mg.
Review Priority Classification:	Standard
Date of Application:	April 27, 2004
Date of Receipt:	April 27, 2004
Our Reference Number:	NDA 21-748

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 June 26, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **February 27, 2005**.

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 note that you have not fulfilled the requirement. We acknowledge receipt of your request for a partial waiver of pediatric studies in children less than 10 years of age, and a deferral of pediatric studies for children 10 years and older for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

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:

NDA 21-748

Page 2

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

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

Sincerely,

*{See appended electronic signature page}*

Jena M. 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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this page is the manifestation of the electronic signature.**  
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/s/

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Jena Weber

5/5/04 05:07:53 PM

# PRESCRIPTION DRUG USER FEE COVER SHEET

## See Instructions on Reverse Side Before Completing This Form

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/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Biovail Laboratories Incorporated Chelston Park, Building 1, Ground Floor Collymore Rock, St. Michael Barbados, West Indies	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-748
2. TELEPHONE NUMBER (Include Area Code)  ( 202 ) 434-4125	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <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)
3. PRODUCT NAME GLUMETZA™ (metformin hydrochloride) extended release tablets	6. USER FEE I.D. NUMBER 4754

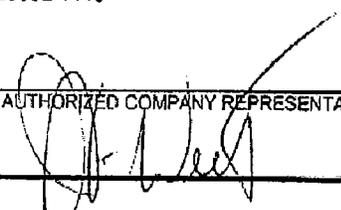
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (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 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 CDER, 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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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Vice-President, Regulatory Affairs	DATE 4/19/2004
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