

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-748

CHEMISTRY REVIEW(S)



NDA 21-748

Glumetza

Metformin Hydrochloride Extended Release Tablets

Biovail Laboratories Incorporated (Biovail)

**Xavier Ysern, PhD
HFD-510**



CHEMISTRY REVIEW



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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-748
2. Review #: 1
3. Review Date: 14-JAN-2004
4. Reviewer: Xavier Ysern, PhD

5. Previous Documents:

<u>Previous Documents</u>	<u>Document Date</u>
IND 57,548	29-DEC-1998
Metformin ER, 500-, and 1000-mg Biovail	
* LOA from DepoMed Inc. authorizing the Agency to cross reference their on behalf of Biovail Corporation is provided on pages 1 and 2 of depomet-loa.pdf (copy of ')	

- | 6. Submission(s) Being Reviewed: | <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|----------------------------------|-------------------------------|----------------------|
| | Original | 27-APR-2004 |
| | Amendment | 20-DEC-2004 |
| | Amendment | 07-JAN-2005 |
| | Amendment | 27-JAN-2005 |
| | Amendment | 15-FEB-2005 |
| | Amendment | 18-FEB-2005 |

7. Name & Address of Applicant:

Name: Biovail Laboratories Incorporated (Biovail)

Address: Chelston Park
Building 1, Ground Floor
Collymore Rock, St Michael
Barbados, West Indies

Representative: John Dubeck, Agent for Biovail laboratories Inc.
Keller and Heckman
101 G Street N.W., Suite 500 West
Washington, DC 20001

Telephone: 202 434-4125

8. Drug Product Name/Code/Type:

- a) Proprietary Name: Glumetza™
- b) Non-Proprietary Name (USAN): Metformin Hydrochloride Extended Release Tables
- c) Code Name/# (ONDC only): --
- d) Chem. Type/Submission Priority:
- | | |
|----------------------|--------|
| Chem. Type: | Type 4 |
| Submission Priority: | S |



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Chemistry Review Data Sheet

9. Legal Basis For Submission: 505(b)(1)
10. Pharmacol. Category: Proposed for the treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise
11. Dosage Form: Tablet
12. Strength/Potency: 500- and 1000-mg
13. Route of Administration: Oral
14. Rx/OTC Dispensed: Rx
15. SPOTS : Not a SPOTS product

16. Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

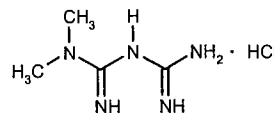
Metformin Hydrochloride

$C_4H_{11}N_5 \cdot HCl$

MW = 129.17 + 36.46 = 165.63

CAS 657-25-9 (free base) 1115-70-4 (hydrochloride)

N,N-Dimethylimidodicarbonimidic diamine monohydrochloride or *N,N*-Dimethylbiguanide HCl



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	LOA date	Holder	Item Referenced	Code ¹	Status ²	Date Review	Comments
Type II							
(	19-MAR-2004	/	/	1	Adequate	14-SEP-2000	--
(	11-MAR-2004	/	/	1	Adequate	17-JAN-2002	--
Type III							
(	26-FEB-2004	/	/	4	Adequate		
(	25-FEB-2004	/	/	4	Adequate		
(	04-MAR-2004	/	/	4	Adequate		
(	03-MAR-2004	/	/	4	Adequate		
(	26-FEB-2004	/	/	4	Adequate		
(	05-MAR-2004	/	/	4	Adequate		
(	09-MAR-2004	/	/	4	Adequate		
(	04-MAR-200	/	/	4	Adequate		
(	08-MAR-2004	/	/	4	Adequate		
(	11-MAR-2004	/	/	4	Adequate		
Type IV							
(	2-MAR-2004	/	/	4	Adequate		
(		/	/	4	Adequate		

DMF letter of authorization (LOA) adequately provided under "dmf-letters.pdf".

⁽¹⁾ Action codes for DMF Table: 1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

⁽²⁾ Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



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Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	23-DEC-2004	Office of Compliance
Biopharm	Dissolution Specification	Pending	
ODS/DMETS LNC	No objection to the proprietary name "Glumetza" (both DMETS and DDMAC) Improvement recommendations to container labels and insert labeling	12-SEP-2004	Kimberly Culley, RPH
Methods Validation	Revalidation of test methods by Agency Laboratories will not be requested	Part of this review	
EA	Categorical Exclusion	Part of this review	
Microbiology	N/A		



CHEMISTRY REVIEW



Executive Summary Section

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved with respect to Chemistry, Manufacturing, and Controls (CMC). The requested expiration period of 36 months is granted only for the 500-mg strength tablets. Due to the limited stability data provided for the 1000-mg strength tablets, a 18 month expiration period is granted for the 1000-mg strength tablets, as requested.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase IV Commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug substance

Metformin, the active component, is an antihyperglycemic agent that belongs to the biguanide class. The mode of action of biguanides is well understood: they act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Metformin is a tautomeric compound of a low molecular weight (129.17 g/mol). Metformin is usually synthesized

Metformin hydrochloride is a white to off-white crystalline compound. The pKa of metformin is 12.4. Metformin is a class 3 (high solubility-low permeability) BCS drug. Metformin hydrochloride, drug substance, is very stable compound with a well characterized stability degradation pathway.

is part of the specifications, and Metformin HCl drug substance, used by the applicant Biovail Laboratories Inc. for the manufacture of the drug product Glumetza™ tablets, is supplied by Both manufacturers synthesize the drug substance

Although metformin hydrochloride have tighter limits for each individual impurity and for total impurities, both manufacturers have similar drug substance specifications meeting USP and Eur. Ph. requirements. Solid metformin hydrochloride is extremely stable. Stability studies from both manufacturers indicated the drug substance is stable up to

Approved drug products using metformin hydrochloride as drug substance include immediate release (innovator and generics) formulations, extended release formulations (Glucophage® XR and Fortamet™), and recently in combination drug products, either with sulfonylureas such as Glyburide and Glipizide (Glucovance™ and Metaglip™ tablets, respectively) or with the thiazolidinedione Rosiglitazone (Avandamet™ tablets).

Drug Product

The drug product, Glumetza™ 500- and 1000-mg Tablets, is an extended release formulation of metformin hydrochloride designed for once a day administration of metformin. Glumetza™ Tablets are designed to provide systemic delivery of metformin over extended period to the upper gastrointestinal (GI) tract where the optimal absorption of metformin occurs. When ingested the tablets rapidly expand in size in the presence of gastric fluid, which allows tablet retention in the stomach during the fed mode, for full delivery, and exits from the stomach in the fasting state. The tablet transits through the intestinal tract, and dissolves away slowly, after the drug has been delivered. The two tablet strengths 500- and 1000-mg are different formulations differing in several excipient components in particular for those

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Glumetza™ 500-mg Tablets consist of a _____ the drug substance metformin hydrochloride plus the excipients polyethylene oxide, hypromellose, microcrystalline cellulose, and magnesium stearate, and a _____ White _____ polymer that _____ controls the release of the active ingredient.

The 1000-mg strength tablet is formulated with _____ metformin _____
_____ The excipients contained in the _____ include _____ crospovidone) _____
_____ silicon dioxide) _____
_____ (glycerol behenate) _____
_____ (ethylcellulose) _____
_____ Dibutyl Sebacate (DBS) _____

During formulation development of the 500-mg formulation _____

The manufacture of the Glumetza™ tablets, includes _____

Glumetza™ Tablets are packaged only in _____ bottles. Tablets are available to patients in 30's (120-cc), and 100's (160 cc) counts for the 500-mg strength and 30's (80 cc) and 90's (215 cc) counts for the 1000-mg strength. all secured with child resistant white _____ caps. _____
_____ Larger capacity _____ bottles of 500's counts (500-mg), and 500's and 1000's counts (1000-mg) are also commercially available to Pharmacies and Health Care Centers. In addition to the ongoing primary stability studies for the 500- and 1000-mg tablets, extensive supportive data was provided for the 500-mg tablets. The supportive stability data for the 500-mg tablets, _____ at 25 °C/60 % RH and _____ 0 °C/75 % RH, was carried out using _____ tablets. The difference in colorant between the _____ tablets (_____ used in the primary stability data lots) and the white tablets (_____ White _____ used in commercial production lots) employed for coating the tablets of the 500-mg strength is a minor difference that affects the appearance but not its stability. The results of the stability studies showed drug product



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Executive Summary Section

compatibility with the packaging materials and reconfirmed the expected stability of metformin hydrochloride in solid oral dosage forms. Consistent with the provided results of the stability study, an expiration period of 36 months has been granted for Glumetza™ 500-mg tablets and 18 months for the 1000-mg tablets, at the recommended storage condition (USP controlled room temperature). Based on the observed degradation trends it is expected that Glumetza™ Tablets would remain within specifications for a significant longer period of time. Those expiration dates were limited by the available provided stability data and could be extended with additional supportive data from the ongoing stability study.

Currently, Bristol-Myers Squibb Pharmaceutical's Glucophage® XR 500-mg and 750-mg Tablets and Andrx's Fortamet™ ER 500-mg and 1000-mg are the two metformin hydrochloride extended release drug products available in the market. Biovail Laboratories Incorporated's Glumetza™ (metformin hydrochloride) 500-mg and 1000-mg Extended Release Tablets will be added to the arsenal of drug products available to patients with type 2 diabetes.

B. Description of How the Drug Product is Intended to be Used

Glumetza™ (metformin hydrochloride) 500-mg and 1000-mg Extended Release Tablets are 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 either as monotherapy or concomitantly with a sulfonylurea or insulin to improve glycemic control in adults. Dosage is individualized based on effectiveness and tolerability, and should not exceed the maximum recommended daily dose of 2000 mg once daily preferably with the evening meal. The usual starting dose is 1000-mg once daily, which in order to maximize therapeutic efficacy must be taken with food preferable in the evening. Dosages increases should be made in increments of 500-mg weekly (to reduce gastrointestinal side effects and to permit identification of the minimum dose required), up to a maximum of 2000-mg once daily with the evening meal. As any other approved metformin containing drug product, in the warning section of the package insert there is a black box cautioning for potential complications due to development of lactic acidosis. Lactic acidosis -characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte unbalance with an increased anion gap- is a rare, but serious (fatal in 50 % of the cases) metabolic complication that can occur due to metformin accumulation (plasma levels > 5 µg/mL) during treatment with the drug product. Glumetza™ tablets should be stored at controlled room temperature. Excessive heat and humidity should be avoided.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls (CMC) are satisfactory. All manufacturing facilities are acceptable. See labeling issues listed on page 62.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date:
Chemistry Team Leader Name/Date
Project Manager Name/Date

Xavier Ysern, PhD 18-FEB-2005
Stephen Moore, PhD
Jena Weber

C. CC Block

60 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling

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/s/

Xavier Ysern
2/22/05 05:54:18 PM
CHEMIST

Stephen Moore
2/22/05 06:18:10 PM
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