CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-460

CHEMISTRY REVIEW(S)

CDER CHEMISTRY REVIEW CDER

NDA 21-460

Metaglip Tablets

Glipizide and Metformin HCl Combination Tablets

Bristol-Myers Squibb Pharmaceutical Research Institute
(BMS)

Xavier Ysern, PhD
HFD-510

CDER CHEMISTRY REVIEW CDER

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Chemistry Review Data Sheet

1. **NDA** 21-460

2. **REVIEW #** 1

3. **REVIEW DATE:** 15-OCT-2002

4. **REVIEWER:** Xavier Ysern

5. **PREVIOUS DOCUMENTS:**

Document(s)	Document Date	
IND — Serial # 021	11-APR-2000	Proposed Biopharmaceutics Plan
IND — Serial # 024	04-AUG-2000	Proposed Long-term Stability Plan

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date	
Original	21-DEC-2001	
Amendment	25-APR-2002	Glipizide EA data
	14-MAY-2002	"Metaglip" proposed tradename
	26-JUN-2002	Additional DP stability data

7. **NAME & ADDRESS OF APPLICANT:**

Name: Bristol-Myers Squibb Pharmaceutical Research Institute (BMS)
Address: P.O Box 4000
Princeton, NJ 08543-4000
Representative: Warren C. Randolph, Director, Metabolic/Endocrine Products
Telephone: (609) 252-5228 Fax: (609) 252-5228

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Metaglip
b) Non-Proprietary Name (USAN): Glipizide and Metformin HCl Tablets
c) Code Name: –
d) Chem. Type/Submission Priority:
- Chem. Type: Type 4
- Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:** –

10. **PHARMACOLOGICAL CATEGORY:** Proposed for the treatment of Type 2 diabetes mellitus as an adjunct to diet and exercise

11. **DOSAGE FORM:** Tablets

12. **STRENGTH/POTENCY:** 2.5-mg/250-mg, 2.5-mg/500-mg, and 5-mg/500-mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. **Rx/OTC DISPENSED:** Rx

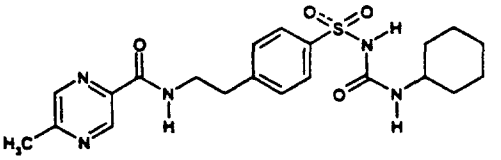
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]: Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WEIGHT:

Glipizide

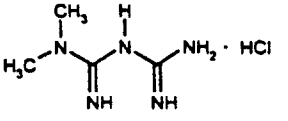
$C_{21}H_{27}N_5O_4S$
MW 445.55
CAS 29094-61-9



1-cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea

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 #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	II			1	Adequate	23-JAN-2002	ANDA 75159
	II			1	Adequate		NDA 20-377 (Glucophage)
	II	L		1	Adequate	20-APR-1998	NDA 21-202 (Glucovance)
	IV	C		1	Adequate	11-OCT-2002	
					Adequate	15-OCT-2002	
	III			4	Adequate		(LOA 30-APR-2001)
	III			3	Adequate	01-APR-1999	
	III			4	Adequate		(LOA 05-NOV-2001)
	III			4	Adequate		(LOA 06-SEP-2001)
	III			4	Adequate		(LOA 05-NOV-2001)
	III			4	Adequate		(LOA 07-NOV-2001)
	III			4	Adequate		(LOA 24-JUL-2001)
				3			DMF Task Force
	III			4	Adequate		(LOA 06-SEP-2001)
	III			4	Adequate		(LOA 01-OCT-2001)
	III			4	Adequate		(LOA 01-NOV-2001)

[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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
BMS's NDA	20-357 (approved 03-MAR-1995)	Glucophage (Metformin HCl) Tablets
BMS's NDA	21-178 (approved 31-JUL-2000)	Glucovance (Glyburide and Metformin HCl) Tablets
BMS's NDA	21-202 (approved 31-OCT-2000)	Glucophage XR (Metformin HCl Modified Release) Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	21-AUG-2002	Office of Compliance
Biopharm	Dissolution Specification. *Phase IV Commitment*	10-OCT-2002	Stephen Johnson, PhD HFD-870
ODS/DMETS LNC	*Tradename Zyphage not acceptable* Tradename Metaglip Acceptable	12-JUL-2002 18-SEP-2002	Samantha Beam, RPh HFD-420 Thomas G. Phillips, RPh HFD-400
Methods Validation	DP Assay (glipizide content and metformin HCl content) and Related Substances (glipizide related and metformin related) — analytical methods will be sent to Agency laboratories for revalidation		
EA	Pending		
Microbiology	N/A		

CHEMISTRY REVIEW

Executive Summary Section

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is **can be approved pending** acceptable BSE-free certificate for the excipient magnesium stearate, acceptable carton and immediate container labels for all dosage forms and satisfactory Environmental Assessment consultative review.

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

There are no CMC Phase IV Commitments.

Biopharm Phase IV Commitments regarding dissolution are as follows:

According to Dr. Johnson's review (Clinical Pharmacology and Biopharmaceutics Reviewer, OPS/OCPB/DPE-2) the use of a pH 7.5 medium for the dissolution of glipizide/metformin HCl combination tablets is unacceptable by the Agency. The data submitted in this application suggests that a pH 6.8 medium should be further investigated and instituted as the regulatory dissolution method. **Biopharmaceutics' requests multipoint dissolution data on each of the tablet strengths using a pH 6.8 dissolution medium, and recommends that the current method will be accepted on an interim basis only. The results from the requested study should be presented to the Agency within 6 months of the Action Letter date** for this application.

II. Summary of Chemistry Assessments

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

The drug product, Metaglip Tablets is a combination product of two active components, glipizide and metformin. These two active components are antihiperglycemic agents that differ in both chemical class and mode of action. Glipizide is a member of the sulfonylurea class and metformin belongs to the biguanide class. Their mode of action is well understood, sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic β cells, whereas biguanides act primarily by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. Due to their complementary mechanisms of action, concurrent administration of glipizide (Glucotrol® (glipizide) tablets) and metformin (Glucophage®, Glucophage® XR, or generic metformin hydrochloride tablets) is frequently prescribed. The combination drug product will facilitate compliance.

Glipizide is a second-generation sulfonylurea compound (second-generation are at least 100 times more potent than first-generation or earlier compounds). The low levels of solvent and water observed in the glipizide drug substance batches, indicate no evidence of solvate or hydrate formation. Also, there are no known polymorphic forms reported in the literature. According to the Biopharmaceutics Classification System (BCS) glipizide is a class 2 (low solubility, high permeability) compound.

Metformin, a tautomeric compound, is a low molecular biguanide synthesized in one reaction step followed by its salt conversion to metformin hydrochloride. It is synthesized as a salt to improve its stability. 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.

Both drug substances have in common: (1) quality control for release is controlled by specifications which are consistent with their respective approved drug substances, glipizide and metformin hydrochloride, (2) particle size is part of their specifications, (3) no evidence of polymorphism, and (4) well characterized stability degradation pathway.

In addition to the USP requirements, [redacted] glipizide is used in the preparation of glipizide and metformin HCl combination tablets to ensure uniform distribution of glipizide and consistent performance of the commercial combination drug product. The tablet formulation was developed to provide fast release of active ingredients. Although [redacted] strengths were developed – 1.25-mg/250-mg, 2.5-mg/250-mg, 2.5-mg/500-mg, 5-mg/500-mg, and [redacted] -mg (gliburide/metformin HCl) – the lower strength (1.25-mg/250-mg) and the [redacted]

strength ( ) are not proposed for approval. The formulation and process used for this product are essentially the same as those used for a BMS previously approved product, Glucovance® (glyburide and metformin HCl combination tablets). An process is used and in addition to the active ingredients, the tablets contain commonly used excipients, including microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, and a film coat. The specification criteria of the combination product are consistent with those for Glucotrol™ (glipizide) tablets and for approved metformin tablets. In addition to debossing, tablets are easily distinguished by size and color.

Metaglip Tablets are packaged in bottles and in blister packages. The drug product is available to patients in (lower strength) and (higher strengths) v bottles containing 100 tablets, secured with child resistant white caps. capacity bottles of and counts are also commercially available to Pharmacies and Health Care Centers. Courtesy samples are distributed in blister packs. In addition to the mentioned packaging configuration stability studies were also carried out in tablets packaged in higher container and counts. The results of the stability studies show the drug product compatibility with the packaging materials and reconfirm the expected stability of glipizide and metformin hydrochloride in solid oral dosage forms.

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

Metaglip™ Tablets is intended to be used orally as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus whose hyperglycemia cannot be satisfactorily managed with diet and exercise. Dosage is based on effectiveness and tolerability, and should not exceed the maximum recommended daily dose of 20 mg glipizide/2000 mg metformin. The usual starting dose is 2.5 mg/500 mg or 5 mg/500 mg daily. Divided doses with gradual dose escalation to avoid hypoglycemia (largely due to glipizide) would allow the determination of the minimum effective dose for adequate control of blood glucose for the individual patient. Metaglip™ tablets should be given with meals to reduce GI effects largely due to metformin. In order to avoid hypoglycemia, the starting dose of Metaglip™ should not exceed the daily doses of glipizide or metformin already been taken. For patients inadequately controlled on glipizide (or another sulfonylurea) monotherapy the usual starting dose of Metaglip™ is 2.5 mg/500 mg to 5 mg/500 mg twice daily with morning and evening meals.

Metaglip™ tablets should be stored at controlled room temperature. Based on the available stability data and statistical analysis, at the recommended storage condition the current expiration dating is 30 months.

C. Basis for Approvability or Not-Approval Recommendation

There are minor CMC deficiencies. All manufacturing facilities are acceptable. Based on the information provided in the submission this application **can be approved** from the Chemistry, Manufacturing and Controls (CMC) standpoint, **pending** acceptable BSE-free certificate for magnesium stearate, acceptable packaging labeling is provided and satisfactory Environmental Assessment consultative review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review	Xavier Ysern
ChemistryTeamLeaderName/Date	Stephen Moore
ProjectManagerName/Date	Jena Weber

C. CC Block

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