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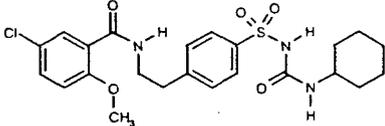
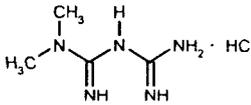
Application Number NDA 21-178/5-004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. Organization CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	2. NDA # 21-178 Approved: 31-JUL-2000
3. Name and Address of Applicant: Bristol-Myers Squibb Company P.O Box 4000 Princeton, NJ 08543-4000 Phone: (609) 818-5221 Fax: (609) 252-6000	4. Supplement SE8-004 Doc. 30-NOV-2001
	5. Name Of The Drug Glucovance™ Tablets
	6. Nonproprietary Name Glyburide & Metformin Hydrochloride
7. Supplement provides a new indication, the use of Glucovance® (glyburide-meformin HCl tablets) with a thiazolidinedione when glycemic control is not obtained with Glucovance® alone.	8. Amendment Doc. 26-SEP-2002

9. Pharmacological Category: Hypoglycemic Agents, treatment of NIDDM.	10. How Dispensed Oral \bar{R}	11. Supporting Documents --
12. Dosage Form Tablets	13. Potencies 1.25-/250-, 2.5-/500- and 5-mg/500-mg	

14. Chemical Name and Structure	
Glyburide C ₂₃ H ₂₈ ClN ₃ O ₅ S MW = 494.0 CAS 10238-21-8 1-[[p-[2-(5-Chloro-o-anisamido)-ethyl]phenyl]sulfonyl]-3-cyclohexylurea	
Metformin Hydrochloride C ₄ H ₁₁ N ₅ · HCl MW = 129.17 + 36.46 = 165.63 CAS 657-25-9 (base) 1115-70-4 (hydrochloride) N,N-Dimethylimidodicarbonimidic diamine monohydrochloride or N,N-Dimethylbiguanide HCl	

15. Comments: This Efficacy Supplement provides for the use of Glucovance® (glyburide-meformin HCl tablets) with a thiazolidinedione when glycemic control is not obtained with Glucovance® alone. To support this claim the applicant conducted a single clinical trial, CV138-055, and published literature. The clinical study, entitled "A Randomized, Double-Blind, Placebo Controlled Trial To Evaluate The Safety And Efficacy Of Rosiglitazone Added On To A Background of Metformin/Glyburide Tablets In Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control On Metformin/Glyburide Therapy", is provided in the submission. There are no changes pertaining to CMC: Drug Substance and Drug Product remain unchanged. As indicated in amendment 26-SEP-2002, due to current market conditions, the use of the active moiety, metformin HCl, is not anticipated to increase in Glucophage, Glucovance and glipizide/metformin HCl products beyond annual volumes previously reported to the Agency. Categorical Exclusion statement, adequately provided in appendix 1 of the amendment. The other active moiety, glyburide, the calculated EEC value is < 1 ppb meeting the categorical exclusion criteria for an environmental assessment according to 21 CFR §25.31(a). In addition, to the sponsor knowledge, no extraordinary circumstances exist (21 CFR §25.15(d)). *CMC regulatory requirements are fulfilled.*

16. Conclusions and Recommendations: Drug Substance and Drug Product remain unchanged. There are no CMC comments to be communicated to the firm. From the chemistry point of view, this supplement can be approved.

17. Reviewer Name (and signature) Xavier Ysern, PhD	Date Completed: 26-SEP-2002
R/D Init. Stephen Moore Chemist Team Leader	filename: /nda/21178s04.doc

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/s/

Xavier Ysern
9/26/02 03:33:35 PM
CHEMIST

Stephen Moore
9/26/02 05:10:09 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**