ATTACHMENT A

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-178
Submission Date(s):	July 21, 2003
Brand Name:	Glucovance™
Generic Name:	Glyburide and metformin HCl tablets
Reviewer:	Sang M. Chung, Ph. D.
Team Leader:	Hae-Young Ahn, Ph. D.
OCPB Division:	DPE-2
OND division:	Metabolic and Endocrine (HFD-510)
Sponsor:	Bristol-Myers Squibb Company
Submission Type:	Pediatric Supplement
Strength(s): (glyburide/metformin)	5/500mg; 2.5/500mg; 1.25/250mg
Indication:	Hypoglycemic agents

1 Executive Summary

The sponsor submitted this pediatric study report for Glucovance® to fulfill the criteria in the Written Request issued on May 29, 2003. The original NDA for Glucovance® (N21-178) was approved on July 31, 2000 with an indication of glycemic control in type 2 diabetic patients. Glucovance® is a fixed combination tablet of glyburide (an insulin secregogue) and metformin (an insulin sensitizer). The Written Request contains Study 1 for pharmacokinetics, and Study 2 for safety and efficacy characterization of the product in pediatric patients. The Study 1 is pertinent to the OCPB and thus included in this review.

The proposed study in the Written Request was to characterize single dose pharmacokinetics of glyburide and metformin in children and adolescents with type 2 diabetes following administration of the lowest strength of Glucovance®. The number of patients should be at least 24 including female and male with ages of 10 to 16 years. Descriptive summary of pharmacokinetic endpoints (such as C_{max}, T_{max}, AUC, CL/F, Vss/F, and $t_{1/2}$) was recommended to be reported.

The sponsor conducted a single dose pharmacokinetic study (Protocol CV138-049) and concluded that glyburide and metformin pharmacokinetics were comparable between children and adolescent patients. In addition, the sponsor made comparison the pediatric pharmacokinetics with those in adults based on historic studies and concluded no

significant difference in glyburide and metformin pharmacokinetics between the two groups.

It seems that glyburide and metformin pharmacokinetics of Glucovance® are not associated with age and body surface area in the pediatric type 2 diabetes though the interpretations are limited by small number of pediatric patients in this study.

In conclusion, the study report has fulfilled recommendations for Glucovance® in the Written Request for pediatric studies.

Optional Intra-Division CPB briefing was held on 11 December, 2003 at 13B17 (Attendee: Drs. Lawrence Lesko, Shiew-Mei Huang, Henry Malinowski, John Hunt, Hae-Young Ahn, and Sang M. Chung) and agreed that the sponsor's conclusions were acceptable.

Glucovance® is currently not recommended for use in pediatric patients because of no significant advantage of Glucovance® over monotherapy of metformin or glyburide, and thus the original labeling will be remaining unchanged in this regard according to the reviewing clinician.