OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-496/S-015	Submission Date(s): 3/14/05
Brand Name	Amaryl®
Generic Name	Glimepiride
Reviewers	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE-2
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Aventis
Submission Type; Code	SE5 (Pediatric Exclusivity); Priority
Formulation; Strength(s)	1, 2, 4 mg tablets for oral administration
Indication	Type 2 diabetes

Executive Summary

The active component of Amaryl is glimepiride, a sulfonylurea that is approved in the treatment of type 2 diabetes.

This submission is a part of the Agency's Written Request dated December 10, 2003 requesting a submission of pediatric information for Amaryl tablets. The sponsor conducted 2 clinical studies and submitted the results in this supplemental NDA. Briefly the 2 studies are:
1. HOE 490/4038: Glimepiride versus metformin as monotherapy in pediatric subjects with type 2 diabetes mellitus: A single blind comparison study.
2. HOE 490/4045: An open-label, multicenter, single dose study to evaluate the pharmacokinetics of glimepiride in pediatric patients with type 2 diabetes.

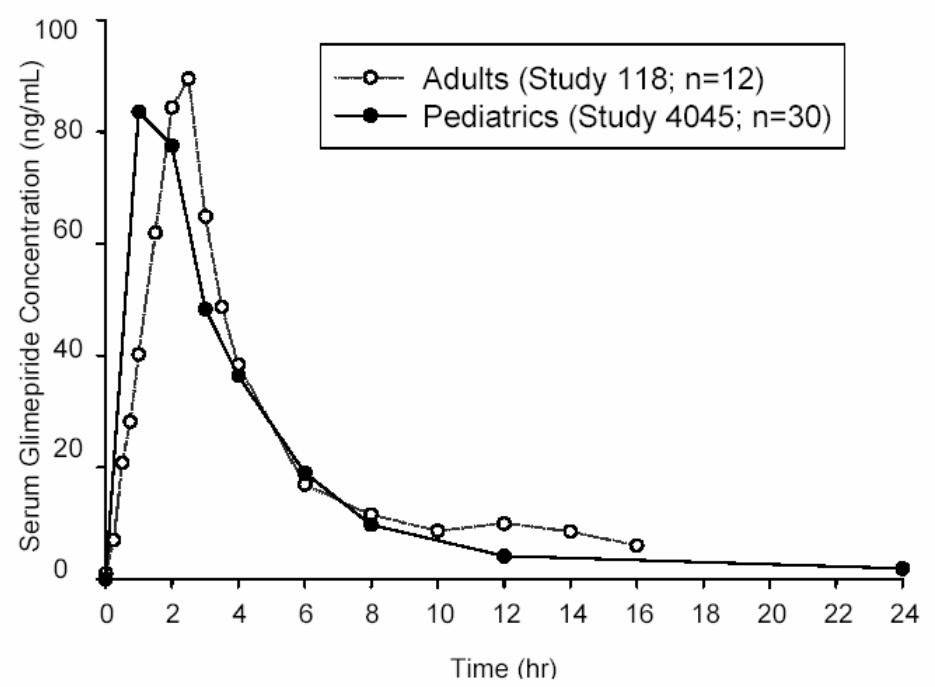
The FDA Pediatric Exclusivity Board granted the applicant Pediatric Exclusivity in June 2005. The Board determined that the applicant had adequately fulfilled the terms of the Pediatric Written Request for Amaryl.

Following oral administration of a single dose of glimepiride (1 mg) after breakfast in pediatric patients, glimepiride was rapidly absorbed with median Tmax of 1 h (range 1-6h). The AUC and C_{max} values were 338.8 ng.h/ml and 102.4 ng/ml respectively. The CL/F and V_{ss}/F was 58.6 ml/min and 13.7 L respectively. Modest negative correlations of

CL with age and weight were observed in this study. However, this does not warrant any dosage adjustments in pediatric patients.

The values obtained in this study were consistent with the PK parameters from prior studies in adult subjects both healthy volunteers (N= 12 from study HOE490/118: dose = 1 mg; AUC =315.2 ng.h/ml; C_{max} =103.2 ng/ml; CL/F = 55.3 ml/min; and V_{ss}/F =10.6 L) and type 2 diabetic patients (Amaryl package insert; dose = 8 mg: C_{max} = 578 ng/ml; CL/F = 52.7 ml/min; and V_{ss}/F =37 L). The mean plasma glimepiride concentration time profiles observed in adults vs. pediatric patients is shown in Figure 1.

Figure 1: Amaryl plasma concentration time profile in pediatric patients and healthy adults.



See medical officer's review for study HOE 490/4038.

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Jayabharathi Vaidyanathan

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