MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	**20496**	**APPLICATION TYPE:**	**Pediatric Study**
SPONSOR:	**Aventis**	**PROPRIETARY NAME:**	**Glimepiride**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**Amaryl**
		ROUTE:	**Oral**
MEDICAL REVIEWER:	**R Misbin**	**REVIEW DATE:**	**Sept 13, 2005**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

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	March 15, 2005	SE-5	Pediatric labeling

Use of AMARYL in pediatric patients with type 2 diabetes is not recommended

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Text should be added to the **Special Populations** section of the label for AMARYL that describes the clinical trial. The efficacy data, change in HbA1c at 24 weeks (Intent To Treat, Last Observation Carried Forward) should be shown separately for naïve and non-naïve patients. Change in body weight and hypoglycemic events (documented by blood glucose < 36 mg/dl) should also be shown.

The following text should be added to the dosage/indications section of the label:

Pediatric: Data are insufficient to recommend pediatric use of AMARYL.

1.2 Recommendation on Postmarketing Actions

No post marketing studies are requested

1.3 Summary of Clinical Findings:

1.3.1 Brief Overview of the Clinical Program

This application contains that results of a trial in which glimepiride was compared to metformin in patients who were naive to treatment, and had baseline HbA1c of 7-12%, or had HbA1c > 7.5% after at least three months of a single oral agent. Patients were between 8-17 years old and were required to be negative for antiislet cell and GAD antibodies and to have stimulated C peptide levels of at least 1.5 ng/mL The initial dose of glimepiride was 1 mg. The dose was titrated to achieve a FBG of <126 mg/dl. The initial dose of metformin was 500 mg bid. Metformin dose escalation to 1000 mg bid was done at 12 weeks in the patients whose FBG exceeded 126 mg/dl. The mean final dose for the per protocol population was 4 mg for glimepiride and 1469 mg for metformin.The mean final dose for the safety population was 3.6 mg for glimepiride and 1373 mg for metformin.

Demographic characteristics were as follows. Median age 14 years, and 33% were male. Approximately 14% of patients were white, 22% African American/ black, 40% Hispanic, and 17% Asian. Approximately 68% were Tanner stage 4 or 5. Mean body weight at baseline was approximately 83 kg.

1.3.2 Efficacy

The primary variable was change in HbA1c at 24 weeks in the per protocol. A margin of 0.3% units was used to test non-inferiority. The results are shown in the following table. Although HbA1c levels fell in both groups, glimepiride failed the non-inferiority test.

HbA1c (%): ANCOVA per protocol population

	Glimepiride			Metformin			Diff: Glimepiride - Metformin		
Time Point	N	Adjusted Mean	SE	N	Adjusted Mean	SE	Adjusted Mean	95% CI	SE
Baseline	81	8.86	0.28	81	9.01	0.28	-0.15	(-0.58; 0.27)	0.21
Change from baseline at:									
Week 12	75	-1.04	0.39	77	-1.37	0.38	0.33	(-0.22; 0.88)	0.28
Week 24	81	-0.95	0.41	81	-1.39	0.40	0.44	(-0.16; 1.05)	0.31

Exploratory Analysis (by FDA) of HbA1c:

Change in HbA1c was analyzed based on whether or not patients had previously received antidiabetic therapy. Excluded from this analysis are patients who took antidiabetic medications **during** the controlled portion of the trial. The results are summarized below. Details are shown in the body of this review and in the FDA statistical review. In naïve patients, treatment with glimepiride or metformin resulted in mean reduction in HbA1c, although glimepiride appeared to be somewhat less effective than metformin. In previously treated patients, there was little change in HbA1c over the course of the study, although patients on metformin tended toward greater reduction in HbA1c than patients on glimepiride.

The difference between naïve patients and previously treated patients requires comment. The protocol stated that there was no washout of previous medication before randomization. A washout of about two months would have been necessary to reestablish a baseline value of HbA1c. Such a long washout would raise ethical issues, particularly in pediatric patients. In essence, patients were switched from one monotherapy to another. So it should not be surprising that there was little net change in HbA1c.

Although it was intended that patients would discontinue previous medication at randomization, some patients inadvertently continued previous metformin treatment during the trial or added an antidiabetic medication other than study drug during the trial. These represent protocol violations and data from these patients are excluded from the analysis.

	HbA1c, unadjusted mean		Adjusted mean change		Difference (Glim-Met)
Previously treated:	Glimepiride	Metformin	Glim	Met	
Baseline	8.84	9.05			
Week 24	8.99	8.82	0.17	-0.23	0.39
Naïve					
Baseline	8.17	8.06			
Week 24	7.10	6.84	-0.97	-1.18	0.21

The efficacy results in the previous table tend to underestimate the clinical effectiveness of metformin vs glimepiride as first line therapy for the following reasons which are discussed in the body of the review:
1 Less than half the patients were titrated to the full dose of metformin which is 1000 mg bid.
2 The efficacy of glimepiride waned from week 12 to week 24. No time-related diminution in the efficacy of metformin was observed

1.3.3 Safety

There were no deaths. Treatment emergent SAE's occurred in 7/142 (4.9%) of patients on glimepiride and 5/142 (3.5%) of patients on metformin. 3 patients on glimepiride and 2 patients on metformin withdrew because of an SAE. Diarrhea was reported in 3.5% of patients on glimepiride and 7.7% of patients on metformin.
There was a mean weight increase of 1.3 kg in glimepiride treated patients from zero to week 24 ($p=0.0005$) but no mean weight change in patients on metformin. There was a mean increase in height of 1 cm in both groups from baseline to endpoint but no difference between the groups.

Hypoglycemic episodes occurred in 16% of glimepiride subjects and 13% of metformin subjects. Episodes were associated with blood glucose <2.0 mmol/L in 4% of glimepiride subjects and 1% metformin subjects. 2 mmol/L = 36 mg/dl.

Overall Assessment: Conclusions and recommendation:

The results of the study support the view that metformin should be used as first line therapy over glimepiride in pediatric patients with type 2 diabetes. Treatment of hyperglycemia with metformin, as measured by reduction in HbA1c, appears less likely to be associated with hypoglycemia. The weight caused by glimepiride is particularly disadvantageous in this population who are already overweight or obese.

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David Orloff

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