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

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
	March 15, 2005	SE-5	Pediatric labeling

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

Table of Contents:

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

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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.

2 Introduction and Background:

The written request (WR), issued initially on January 2, 2002, described a randomized clinical trial that compared glimepiride monotherapy to metformin monotherapy . Patients were to have been naïve to antidiabetic therapy. The initial dose of glimepiride was 1mg. This dose was to be titrated to achieve a fasting blood glucose (FBG) of < 126 mg/dl*. The dosing schedule for metformin was 500 mg bid initially and 1000 mg bid for weeks 12 the 24 (end of trial). Having not been the medical officer at the time the WR was issued, I cannot be certain about what was intended by the different dosing schedules indicated in the WR. Based on my conversations with Dr Koller (the original medical officer) and my own understanding of the clinical situation, I shall try to present the reasoning behind the terms of the WR:

Metformin is the only oral antidiabetic agent that has been shown to decrease mortality. It does not cause weight gain, has a generally favorable effect on plasma lipids, and rarely causes hypoglycemia when used alone. For these reasons, it is considered the treatment of choice for type 2 diabetes in children, nearly all of whom are obese. The problem with metformin is that certain patients will not tolerate a full dose (1000 mg bid) because of gastrointestinal discomfort. Compliance is a problem, particularly in children. I believe one of the goals of the study in the WR was to compare the proportion of children who would not tolerate (or be complaint) to a full dose of metformin to the proportion of children who would develop hypoglycemia on glimepiride.

The WR was revised at the Sponsor's request because of difficulty recruiting patients.

This application contains the results of a trial in which glimepiride was compared to metformin in patients who were naive to treatment, and had baseline HbA1c values of 7-12%, or had had HbA1c > 7.5% after at least three months of a single oral agent. There was a two week "stabilization" period, but patients on antidiabetic agents could be randomized without washout. 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 dose glimepiride was I mg initially, and 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 those 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.

* The WR originally specified FPG < 140mg/dl. This was later changed to FBG <126mg/dl. Since FPG is normally about 10% higher than FBG, these numbers are essentially the same.

3 Findings from Other disciplines: N/A

4 Description of Data Sources and Integrity

The application contains data from one controlled clinical trial in pediatric patients with type 2 diabetes.
The review was conducted of the hard copy of the NDA. Routine inspections of sites were not performed. The trials appear to have been conducted in accordance with acceptable ethical standards. The financial disclosure documentation appears adequate.

The consent document states "You will be paid $___ for each visit completed". The amount is left blank because it varied depending on the site. Review of the actual amounts that subjects received disclosed a range of zero to $420 ($60 for each of seven visits). The median amount was $175.

The Sponsor, Sanofi Aventis, submitted debarment documents on July 13, 2005 The financial disclosure documents were submitted with the original sNDA on March 15, 2005. I have examined these documents and found them to be acceptable. The debarment statement indicated that Sanofi Aventis has not used any person debarred pursuant to section 306 of the Federal Food, Drug and Cosmetic Act.
The following financial disclosure information has been submitted:
1 Form OMB No. 0910-0396. The applicant certifies that has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study.
2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in .
3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from .

5 Clinical Pharmacology - N/A

6 Review of Efficacy:

The demographic characteristics at baseline were as follows:

Both groups: Median age 14 years, 33% male,

Metformin: 15% white, 22% African American/ black, 39% Hispanic, 15% Asian
Glimperide: 13% white, 22% African American/ black, 40% Hispanic, 17% Asian

Tanner stage	One	Two	Three	Four	Five
Glimepride (n=142):	7%	6%	17%	30%	39%
Metformin (n=142):	8%	9%	17%	26%	41%

The mean final dose for the per protocol population was 4 mg for Glimepiride and 1469 mg for metformin

The primary variable was change in HbA1c at 24 weeks in the per protocol population. 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. It should also be noted that the maximal efficacy of Glimepiride was observed at 12 weeks and waned somewhat to week 24. By contrast, the efficacy of metformin was maintained through 24 weeks.

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

Results for FBG are shown in the table that follows. These data are largely consistent with the changes in HbA1c described earlier.

Blood Glucose (mg/dl) ANCOVA per protocol population

	Glimepiride			Metformin			Diff: Glimepiride - Metformin		
Time Point	**N**	**Adjusted Mean**	**SE**	**N**	**Adjusted Mean**	**SE**	**AdjustedMean**	**95% CI**	**SE**
Baseline	78	171.4	12.77	78	166.2	12.46	5.2	(-14.0; 24.4)	9.76
Change from baseline at									
Week 4	78	-9.5	9.95	78	-15.3	9.72	5.8	(-9.2; 20.8)	7.61
Week 8	78	-15.5	9.78	78	-12.4	9.55	-3.1	(-17.8; 11.7)	7.48
Week 12	78	-15.6	10.40	78	-13.5	10.15	-2.1	(-17.8; 13.5)	7.95
Week 18	78	-23.1	10.29	78	-31.2	10.05	8.1	-7.4; 23.6)	7.87
Week 24	78	-22.5	11.21	78	-35.5	10.94	13.0	-3.9; 29.9)	8.57

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Lipids (Sponsor's text)

Total cholesterol increased by a mean of 0.206 mmol/L at Week 24 with glimepiride, which, although clinically a small increment, was statistically significant (*P = 0.0123*). Total cholesterol decreased by a mean of 0.004 mmol/L with metformin, which was not significant. There was no significant difference between treatment groups in changes in total cholesterol from baseline. No significant changes from baseline in HDL cholesterol were observed in either treatment group. A nonsignificant increase from baseline in mean LDL was observed with glimepiride and a nonsignificant decrease was observed with metformin. The difference between the 2 treatments in changes in LDL from baseline was statistically significant (*P = 0.0415*)..When LDL cholesterol values were imputed where data were not reported by the laboratory, the difference between the 2 treatment groups was not significant. Increases from baseline in triglycerides were not significant with glimepiride but were statistically significant (*P = 0.0368*) with metformin. The difference between the 2 treatment groups in their change from baseline, however, was not significant.
The ratio of LDL:HDL cholesterol increased from baseline to a nonsignificant extent with glimepiride but decreased significantly with metformin (*P = 0.0025*). The difference between the 2 treatment groups in changes in LDL:HDL cholesterol ratios was statistically significant *(P = 0.0366*). This treatment difference in LDL:HDL ratios may be attributed to the mean increase in LDL from baseline in the glimepiride group compared with the mean decrease in the metformin group. Mean changes from baseline in VLDL cholesterol were not significant for either the glimepiride or metformin group, and there was no significant difference between the 2 treatments in change in VLDL from baseline.

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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 other than study drugs **during** the controlled portion of the trial. The results are shown in two tables below taken from the FDA statistical review. In naïve patients, treatment with glimepiride or metformin resulted in mean reduction in HbA1c, although glimepiride appeared to be 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 in the efficacy 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 two months or more would have been necessary to reestablish a baseline value of HbA1c. Such a long washout would raised 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 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.

Table 1 HbA1c (%): analysis of covariance (ANCOVA) results - excluding subjects taking anti-diabetic medication

	Unadjusted Mean (SD)				Adjusted Mean Change from Baseline (SE)		Difference: Glimepiride - Metformin		
	N	Glimepiride	N	Metformin	Glimepiride	Metformin	Adjusted Mean	95% CI	p-value
Per Protocol									
Baseline	79	8.56 (1.3)	80	8.69 (1.4)					
Week 12	73	7.92 (1.9)	76	7.58 (2.1)	-1.03 (0.4)	-1.37 (0.4)	0.34	(-0.22, 0.90)	0.2319
Week 24	79	7.86 (2.1)	80	7.45 (2.1)	-0.95 (0.4)	-1.38 (0.4)	0.43	(-0.18, 1.05)	0.1663
Intent-to-Treat									
Baseline	127	8.46 (1.5)	126	8.51 (1.5)					
Week 12	116	7.94 (1.9)	121	7.84 (2.4)	-0.66 (0.3)	-0.75 (0.3)	0.09	(-0.35, 0.54)	0.6892
Week 24 (LOCF)	127	7.92 (2.1)	126	7.73 (2.4)	-0.63 (0.3)	-0.83 (0.3)	0.20	(-0.28, 0.68)	0.4195
Safety Population									
Baseline	135	8.42(1.5)	137	8.60 (1.6)					
Week 12	116	7.94 (1.9)	121	7.84 (2.4)	-0.66 (0.3)	-0.75 (0.3)	0.09	(-0.35, 0.54)	0.6892
Week 24 (LOCF)	135	7.92 (2.1)	137	7.89 (2.4)	-0.55 (0.3)	-0.70 (0.3)	0.15	(-0.30, 0.60)	0.5123

Analysis of covariance with treatment, country, and tanner stage effects and the corresponding baseline value as covariate was used for the change from baseline
Source: re-analysis of data and from sponsor‘s 2ef0001tx.doc and 2ef0002tx.doc

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Table 2: HbA1c (%): Analysis of Covariance (ANCOVA) Results by Previous Anti-diabetic Use, removing subjects that have ongoing anti-diabetic treatment during study period.

			Unadjusted Mean (SD)			Adjusted Mean Change from Baseline (SE)		Difference: Glimepiride - Metformin		
Population	Subgroup	N	Glimepiride	N	Metformin	Glimepiride	Metformin	Adjusted Mean	95% CI	p-value
Per Protocol	Previously AB Treated									
	Baseline	33	8.76 (1.4)	36	9.16 (1.3)					
	Week 12	32	8.80 (1.9)	36	8.53 (2.5)	0.14 (0.8)	-0.29 (0.8)	0.43	(-0.53, 1.39)	0.3706
	Week 24 (LOCF)	33	9.00 (2.2)	36	8.39 (2.4)	0.75 (0.9)	-0.13 (0.9)	0.88	(-0.19, 1.94)	0.1041
	Not Previously Treated									
	Baseline	46	8.42 (1.3)	44	8.31 (1.4)					
	Week 12	41	7.05 (1.6)	40	6.74 (1.2)	-1.43 (0.4)	-1.86 (0.4)	0.43	(-0.18, 1.04)	0.1631
	Week 24 (LOCF)	46	7.05 (1.7)	44	6.68 (1.4)	-1.47 (0.4)	-1.79 (0.4)	0.32	(-0.35, 0.98)	0.3447
ITT	Previously AB Treated									
	Baseline	55	8.84 (1.5)	57	9.05 (1.5)					
	Week 12	51	8.79 (2.0)	57	8.97 (2.8)	0.01(0.6)	-0.004 (0.6)	0.02	(-0.75, 0.78)	0.9647
	Week 24 (LOCF)	55	8.99 (2.2)	57	8.82 (2.7)	0.17 (0.7)	-0.23 (0.7)	0.39	(-0.44, 1.22)	0.3488
	Not Previously Treated									
	Baseline	72	8.17 (1.5)	69	8.06 (1.4)					
	Week 12	65	7.28 (1.6)	64	6.83 (1.3)	-0.93 (0.3)	-1.28 (0.2)	0.35	(-0.10, 0.80)	0.1324
	Week 24 (LOCF)	72	7.10 (1.6)	69	6.84 (1.6)	-0.97 (0.3)	-1.18 (0.3)	0.21	(-0.29, 0.70)	0.4136
Safety	Previously AB Treated									
	Baseline	58	8.81 (1.5)	62	9.15 (1.5)					
	Week 12	51	8.79 (2.0)	57	8.97 (2.8)	0.01 (0.6)	-0.004 (0.6)	0.02	(-0.75, 0.78)	0.9647
	Week 24 (LOCF)	58	8.97 (2.1)	62	8.93 (2.7)	0.22 (0.6)	-0.11 (0.6)	0.33	(-0.45, 1.10)	0.4048
	Not Previously Treated									
	Baseline	77	8.13 (1.5)	75	8.14 (1.5)					
	Week 12	65	7.28 (1.6)	64	6.83 (1.3)	-0.93 (0.3)	-1.28 (0.2)	0.35	(-0.10, 0.80)	0.1324
	Week 24 (LOCF)	77	7.13 (1.6)	75	7.02 (1.7)	-1.00 (0.3)	-1.11 (0.3)	0.11	(-0.36, 0.59)	0.6424

Analysis of covariance with treatment, country, and tanner stage effects and the corresponding baseline value as covariate was used for the change from baseline
Source: Re-analysis of data and sponsor's results 2ef0001ty.doc, 2ef0002ty.doc, 2ef0001tz.doc, 2ef0002tz.doc,

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Comment on Trial Design

The written request (WR), issued initially on January 2, 2002, described a randomized clinical trial that compared glimepiride monotherapy to metformin monotherapy. Patients were to have been naïve to antidiabetic therapy. The dose of glimepiride was to be titrated to achieve a fasting blood glucose (FBG) of < 126 mg. /dl* The dosing schedule for metformin was 500 mg bid initially and 1000 mg bid for weeks 12 the 24 (end of trial). At the Sponsor' request, the WR was later amended to allow inclusion of patients who had previously received antidiabetic drugs.
I shall try to present the reasoning behind the terms of the WR and the importance of the changes that were subsequently made.

Dosing:

Metformin is the only oral antidiabetic agent that has been shown to decrease mortality. It does not cause weight gain, has a generally favorable effect on plasma lipids, and rarely causes hypoglycemia when used alone. For these reasons, it is considered the treatment of choice for type 2 diabetes in children, nearly all of whom are obese. The problem with metformin is that certain patients will not tolerate a full dose (1000 mg bid) because of gastrointestinal discomfort. Compliance is a problem, particularly in children. One of the goals of the study in the WR was to compare the proportion of children would not tolerate (or be complaint) to a full dose of metformin to the proportion of children who would develop hypoglycemia on glimepiride.

For glimepiride, the dose escalation was to be based on efficacy. For metformin, we expected that dose escalation would be limited by gastrointestinal intolerance. The results of the study are less useful than they would have been had more patients received the full dose (2000 g per day) of metformin

Dosing of glimepiride, like all sulfonylureas, must be titrated to prevent hypoglycemia. The escalated dosing schedule for metformin (500-mg bid initially followed by 1000 mg bid after 12 weeks) was designed to enable as many patients as possible to achieve a full dose. Titrating the dose of metformin based on FBG, as was done by the Sponsor, reduced the proportion of patients who achieved a full dose. This limited the ability to detect a difference between glimepiride and metformin.

The findings listed below illustrate that study drugs could have been titrated more aggressively without jeopardizing patient safety. On the other hand, the Sponsor has correctly pointed out that it would have been inappropriate to increase the dose of metformin without **some** glucose goal. In the absence of instruction from FDA, it is hard to criticize the Sponsor for using the same glucose goal for metformin as for glimepiride.

1 The mean fasting glucose at 24 weeks for the per protocol population was approximately 149 mg/dl for glimepiride and 131 mg/dl for metformin. Therefore, the Sponsor fell short of their titration goal of FBG < 126 mg/dl even in most per protocol patients. The goal set by the American Diabetes Association for adults is 90-130 mg/dl.

2 The mean HbA1c at 24 weeks for the per protocol population was about 7.9% for glimepiride and 7.6% for metformin. The goal set by the American Diabetes Association for adults is <7%.

3 Diarrhea was the most frequent gastrointestinal AE in metformin-treated patients but this was reported in only 7.7%. Abdominal pain was reported in only 3.5%. SAE's and withdrawals due to AE occurred in less than 5% with both treatments. Thus, the dose of metformin could probably have been increased to 1000 mg bid in most patients as put forth in the WR.

Inclusion of non-naïve patients:

It has only recently been realized that type 2 diabetes is important to diagnosis in adolescent patients. Particularly in Latino, African American and native American populations, there is probably a reservoir of undiagnosed patients who would benefit personally from participation in a clinical trial. This benefit does not pertain to patients who have already been diagnosed and have received antidiabetic treatment. To the contrary, it could be argued that including previously treated patients is exploitation. Glimepiride, like other sulfonylureas, causes weight gain and hypoglycemia when used to treat type 2 diabetes in adults. That the same effects were seen in adolescent patients was not a surprise. Even leaving ethical issues aside, the inclusion of previously treated patients muddied the data analysis for at least two reasons:

1) A washout of two months or more would have been necessary to reestablish the baseline HbA1c*.
2) The response to previous therapy may have influenced the response to treatments being tested.

* see Review of pediatric trial of Avandia

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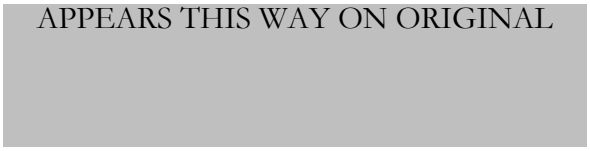
7 Review of Safety

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.

In the safety population at 24 weeks, there was a mean weight increase of 1.3 kg in glimepiride treated patients (n=134, p=0.0005) but minimal mean weight change (-0.14 kg) in patients on metformin (n=131, NS). There was a mean increase in height of 1 cm in both groups from baseline to endpoint but no difference between the groups. Results in the per protocol population were virtually identical.



Treatment emergent adverse events (TEAEs) are shown in the following table.

Preferred term name	Number (%) of subjects							
	All TEAEs				Possibly Related TEAEs			
	Glimepiride(N=142)		Metformin (N=142)		Glimepiride (N=142)		Metformin (N=142)	
SUBJECTS WITH TEAES	84	59.2%	82	57.0%	11	7.70%	19	13.4%
Headache	15	10.6%	17	12.0%	0	0.0%	3	2.1%
Upper respiratory tract infection	10	7.0%	9	6.3%	0	0.0%	0	0.0%
Nasopharyngitis	9	6.3%	10	7.0%	0	0.0%	0	0.0%
Hyperglycemia	8	5.6%	3	2.1%	4	2.8%	1	0.7%
Abdominal pain upper	6	4.2%	1	0.7%	2	1.4%	1	0.7%
Diarrhea	5	3.5%	11	7.7%	1	0.7%	6	4.2%
Abdominal pain	5	3.5%	5	3.5%	2	1.4%	2	1.4%
Influenza	5	3.5%	3	2.1%	0	0.0%	0	0.0%
Pharyngitis	5	3.5%	1	0.7%	0	0.0%	0	0.0%
Ear infection	5	3.5%	0	0.0%	0	0.0%	0	0.0%
Pyrexia	4	2.8%	0	0.0%	0	0.0%	0	0.0%
Gastroenteritis	3	2.1%	5	3.5%	0	0.0%	0	0.0%
Viral infection	3	2.1%	4	2.8%	0	0.0%	0	0.0%
Epistaxis	3	2.1%	3	2.1%	0	0.0%	0	0.0%
Sinusitis	3	2.1%	3	2.1%	0	0.0%	0	0.0%
Constipation	3	2.1%	1	0.7%	0	0.0%	0	0.0%
Fatigue	3	2.1%	1	0.7%	0	0.0%	0	0.0%
Pharyngitis streptococcal	3	2.1%	0	0.0%	0	0.0%	0	0.0%
Rash	3	2.1%	0	0.0%	0	0.0%	0	0.0%
Nausea	2	1.4%	5	3.5%	1	0.7%	4	2.8%
Vomiting	1	0.7%	5	3.5%	0	0.0%	1	0.7%
Dysmenorrhea	1	0.7%	4	2.8%	0	0.0%	0	0.0%
Dizziness	1	0.7%	3	2.1%	0	0.0%	1	0.7%
The numbers in each column cannot be added because a subject may have had more than 1 adverse event.								

Hypoglycemia:

The Sponsor summarizes the hypoglycemia findings as follows:

In summary, 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 and 1% metformin subjects. A severe episode treated with countermeasures occurred in 1 subject of each group. The differences between groups were not significant.

Comment:

The one patient on metformin who had an episode of assisted hypoglycemia was a 13 year old boy with Prader Willi syndrome who was on 500 mg metformin from July 7 2003 through November 17 2003. His HbA1c at randomization and endpoint were 6.0% and 6.1% respectively. On (b) (6) he was reported to have a "mild" seizure associated with a glucose of 23 mg/dl. The episode was said to have lasted three days. Other glucoses were recorded in the 40's. He was withdrawn from the study one week later.

The risk of hypoglycemia appears greater with Glimepiride than with metformin, particularly when one considers that HbA1c reduction appeared greater with metformin. This result is consistent with findings of other studies. In the footnote below, I review findings of hypoglycemia in other trials in which metformin monotherapy was compared to sulfonylurea monotherapy or rosiglitazone montherapy. Also, included are the hypoglycemia findings of the placebo-controlled trial of metformin in pediatric patients. When taken together, I believe it is reasonable to conclude that metformin monotherapy rarely causes hypoglycemia, and is certainly less likely to cause hypoglycemia than sulfonylureas. Given the rarity of Prader Willi syndrome, the report of “assisted hypoglycemia” in this one metformin patient should not be generalized.

Metformin vs Glyburide in Adult patients (first line therapy from Glucovance trials):
Hypoglycemia as an adverse events was reported in 3% of patients on placebo, 3% on metformin and 21% on Glyburide. There were approximately 160 patients in each arm. Hypoglycemia documented by glucose < 50 mg/dl was reported by one patient on placebo, zero on metformin and 10/160 (6%) of patients on Glyburide, or which five patients (3%) withdrew.

Metformin vs Glipizide in Adult patients (first line therapy)
Symptomatic hypoglycemia, confirmed with finger stick glucose < 50mg/dl was reported in 3% of patients on Glipizde (n-84) and zero patients on metformin (n=76).

Metformin vs placebo in Pediatric patients:
1/42 on metformin had asymptomatic hypoglycemia (BG=39 mg/dl). No reports of hypoglycemia as severe AE, AE leading the withdrawal, or requiring assistance.

Metformin vs Glyburide in Pediatric patients:
Hypoglycemia was reported as an AE in 2/55 (3.6%) of patients on metformin and 3/52 (5.8%) of patients on glyburide. One of the metformin patients and one of the Glyburide patients required assistance.

Rosiglitazone vs metformin in Pediatric patients:
Hypoglycemia as an AE was reported in 5/101 patients on Metformin and 4/99 patients on Rosiglitazone. But there were no reports of hypoglycemia as a serious adverse event in either group and no withdrawals related to hypoglycemia.

8 Dosing, Regimen, and Administrative Issues:

Labeling:
The Sponsor has proposed the following labeling:

Pediatric Use

(b) (4)

This proposed labeling leaves out the following information:

1 The data do not establish that AMARYL is non-inferior to metformin with respect to reducing HbA1c.

2 There was a mean weight gain of 1.3 kg in patients treated with AMARYL (p=0.0005). On average, there was no change in weight for patients treated with metformin.

3 Hypoglycemic events, as documented by blood glucose values <36 mg/dL (2 mmol/L) , occurred in 4% of patients treated with AMARYL and 1% with metformin).

4 Diarrhea was reported by 3.5% of patients treated with AMARYL and 7.7% with metformin.

The Sponsor should be requested to revise the label as follows:

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, ITT LOCF, should be shown for naïve and non-naïve patients. The following safety data should also be shown: Change in body weight and hypoglycemic events (documented by blood glucose < 36 mg/dl).

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

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

9 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.

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, ITT LOCF, should be shown for naïve and non-naïve patients. The following safety data should also be shown: Change in body weight and hypoglycemic events (documented by blood glucose < 36 mg/dl).

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

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Misbin
9/15/2005 02:38:55 PM
MEDICAL OFFICER

David Orloff
9/15/2005 05:05:39 PM
MEDICAL OFFICER
Concur.