Executive Summary

I. Recommendations:

The Glucovance label currently says

Under Pediatric use:

"Safety and effectiveness of GLUCOVANCE in pediatric patients have not been established."

The Sponsor proposes to change this to:

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This should be revised to read:

"The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. The mean HbA1c at baseline in these patients was about 7.8%. GLUCOVANCE was not shown statistically to be superior to either metformin or glyburide with respect to reducing Hb_{A1c} from baseline . No unexpected safety findings were associated with GLUCOVANCE in this trial."

The following statement, presently in the Dosage and Administration Section,

"GLUCOVANCE is not recommended for use during pregnancy or for use in pediatric patients" can be modified to read:

"GLUCOVANCE is not recommended for use during pregnancy."

II. Summary of Clinical Findings

The Sponsor submitted the results of one 26-week, randomized, three-arm, active-controlled, double-blind trial. The three arms were Glucovance, metformin alone, and glyburide alone.

167 patients with type 2 diabetes, ages 9-16, were randomized and received double-blind medication. 87 (52%) patients had never previously received antidiabetic medications.

The mean age was 13.7 years. They were 35% male and 65% female. Distribution by ethnicity was 62% white, 21% black, 13% Hispanic, 4% Asian, 1% other.
Patients were > 50th percentile for weight and did not have adequate glycemic control on exercise/diet with or without a single oral hypoglycemic drug. Inadequate glycemic control was defined as HbA1c > 6.4% and mean fasting glucose (MFG) < 350 mg/dl.

Drug-naïve patients had to have HbA1c between 6.4% and 14% at screening. After a one week lead-in, drug-naïve patients with MFG < 350 mg/dl were randomized. Non-naive patients (on a single oral hypoglycemic agent) had to have HbA1c between 6.4% and 9% at screening. They underwent a variable 2 – 4 week washout period. During the washout, subjects were eligible for randomization if the MFG was 200-350 mg/dl.

The primary efficacy variable was change in HbA1c. The study was designed to test the superiority of Glucovance to each of the monotherapies. The ITT population consisted of the 160 subjects who had HbA1c measurements at baseline and endpoint.

Efficacy:

The major efficacy findings are shown in the table below. Glucovance (Metformin/Glyburide) was not superior to metformin or glyburide monotherapy with respect to reduction in HbA1c.

	MET/GLY	MET	GLY
HbA1c	N=57	N=54	N=49
Baseline	7.85	7.99	7.70
Week 26/last	7.05	7.46	6.80
Adj mean change*	**-0.80**	**-0.48**	**-0.96**
FPG			
Baseline	154	176	154
Week 26/last	135	143	135
Adj mean change*	**-23**	**-25**	**-23**
Body weight			
Baseline	80.1	79.7	78.9
Week 26/last	81.3	79.7	81
Adj mean change*	**+1.24**	**0.00**	**+2.08**
Mean Final Dose	**623mg/3.1mg**	**1500 mg**	**6.5 mg**

* There were no statistically significant differences between Glucovance and the monotherapies.

These results appear to be at variance to the results found in the original Glucovance NDA in trials conducted in adult patients with type 2 diabetes. These data are summarized* in the tables below for the purpose of comparison to data from the pediatric trial shown above.

Studies in Adults:

Mean Change In HbA1c

	Met/Gly	Met	Gly
HbA1c, baseline	8.22 n=149	8.23 n=141	8.14 n=142
HbA1c, change	-1.48	-1.03	-1.24
Final dose, mg	577/2.78	1307	5.3

* To facilitate comparison to the pediatric study, only data from the Metformin/Glyburide 250/1.25 mg, metformin monotherapy and glyburide monotherapy arms are shown. The adult study also had a placebo arm, and a Metformin/Glyburide 500 mg/2.5 mg arm. Data from these arms are not included in this table but are shown in later tables.

In the original NDA, Glucovance was found to be superior to both metformin and glyburide administered as monotherapies, and was therefore approved for initial therapy in adults with type 2 diabetes. However, the superiority of Glucovance was largely driven by data from patients with HbA1c of 9% and above (see table below).

Studies in Adults: Change in HbA1c according to Baseline HbA1c

HbA1c, baseline	Met/Gly		Met		Gly	
<8	-0.90	n=71	-0.73	n=68	-0.93	n=77
8-8.9	-1.31	n=35	-1.26	n=39	-1.27	n=34
9.0-9.9	-2.40	n=30	-1.50	n=23	-1.89	n=22
>9.9	-3.21	n=13	-1.28	n=11	-1.87	n=9

For patients with HbA1c under 9% there was no advantage of Glucovance over the individual monotherapies. That very few pediatric patients had this degree of hyperglycemia may well account for the difference between the results of the pediatric trial and the original trial in adults. As shown in an earlier table, the mean HbA1c values at baseline in the pediatric study were about 7.7 – 8%.

A second difference between the pediatric trial and the adult trial was that the adult trial allowed only treatment-naïve patients to be randomized. The FDA statistical review makes the point that Glucovance appeared better than the monotherapies in naïve but not in non-naïve pediatric patients.

	Met/Gly	Met	Gly
Naïve	-1.35	-0.92	-1.23
Non-naïve	-0.09	-0.20	-0.68

That all three treatments appeared less effective in the non-naïve patients may be due to the fact that these patients did not receive optimally effective doses of study medications.

Safety:

No unexpected safety issues emerged during the study. There were only small differences in the spectrum and frequency of adverse events among the three treatment arms. Due to dose-sparing of metformin, patients on Glucovance appeared to have somewhat fewer gastrointestinal complaints than patients on metformin monotherapy. Patients on metformin monotherapy gained less weight. As expected, hypoglycemia appeared related to glyburide.

Conclusions:

Little if any new or unexpected information about the use of Glucovance in children was learned from this trial. Although there may appear to be differences in efficacy between children and adults, these apparent differences likely reflect differences in trial design and in the baseline clinical characteristics (e.g., severity of diabetes) of the patients enrolled in the trials.

In adult patients, an important use of Glucovance is first line therapy for moderately severe hyperglycemia. Patients with moderately severe hyperglycemia were not studied in the pediatric trial. Based on the experience with adults, it is likely that Glucovance would have been more effective in pediatric patients with moderately severe hyperglycemia than in those with mild hyperglycemia (as enrolled in the trial), and this combination therapy might save children with type 2 diabetes from being started on injections of insulin. The revised label should not preclude physicians from considering this possibility. It is therefore important to indicate that the negative results in this trial pertain to patients whose mean HbA1c levels at baseline were approximately 7.8%.

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David Orloff

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