EXECUTIVE SUMMARY

Application Type	NDA (new drug application) pediatric supplement
Submission Number	**NDA 21-071 S-015 SE5**
Submission Code	N-000
Letter Date	September 30, 2004
PDUFA Goal Date	3/31/05
Reviewer Name	Joanna K. Zawadzki M.D.
Review Completion Date	4/12/05
Established Name	rosiglitazone maleate
Trade Name	*Avandia* ®(GlaxoSmithKline)Tablets
Therapeutic Class	Hypoglycemic Agent (3031450)
Applicant	GlaxoSmithKline
Priority Designation	P
Formulation	rosiglitazone maleate 2, 4, 8 mg
Dosing Regimen	once daily or twice daily (rosiglitazone 2 and 4 mg twice daily regimen was used in this study)
Proposed Indication	Treatment of Type 2 Diabetes Mellitus, specifically "monotherapy for the treatment of pediatric patients with type 2 diabetes mellitus aged 10 years and older whose hyperglycemia is not adequately controlled on a regimen of diet and exercise alone (drug-naïve)"
Intended Population	Children (ages 10-17) with type 2 diabetes mellitus
Relevant NDA(s)	**NDA 21-071** (rosiglitazone maleate [BRL-049653-C] *Avandia* ®,GlaxoSmithKline) approved 5/25/99
Relevant IND(s)	**IND 43,468**
Medical Team Leader and Division Director	David G. Orloff, M.D.
Statistical Reviewer	Joy Mele, M.S.
Project Manager	Jena Weber

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RECOMMENDATION ON REGULATORY ACTION

GlaxoSmithKline has submitted data from a multicenter, randomized, active-controlled clinical study (Study BRL-049653/207, subsequently referred to as Study 207) to support FDA's granting of Pediatric Exclusivity, a proposed new indication for use of rosiglitazone (AVANDIA®), a peroxisome proliferator activated receptor gamma agonist, of the thiazolidinedione class, in children with type 2 diabetes mellitus, as well as additional proposed pediatric labeling. Pediatric Exclusivity was granted in December 2004. On the basis of an analysis of the subgroup of treatment-naïve patients, constituting approximately half of the randomized patients, the sponsor proposed an indication for rosiglitazone for the treatment of children ages 10-17 with type 2 diabetes mellitus who are naïve to prior pharmacologic therapy for diabetes. Because of limitations of the study precluding formal statistical inference of efficacy relative to metformin (the active comparator) and certain adverse effects associated with rosiglitazone therapy, particularly weight gain, the data are inadequate to support the requested pediatric indication. Data from this study that address efficacy as well as safety should be included in the prescribing information to be available to clinicians. The label revisions are under discussion with the sponsor.

SUMMARY OF CLINICAL FINDINGS

Brief Overview of Clinical Program

The FDA issued a Written Request to assess the safety and efficacy of rosiglitazone (*Avandia*®, GlaxoSmithKline), a thiazolidinedione approved for the treatment of adult Type 2 diabetes mellitus on 5/25/1999, for the treatment of type 2 diabetes in pediatric patients on 2/1/2000, which was subsequently amended on 5/24/2002 and 12/15/2003, at the sponsor's request. In response to the Written Request, the sponsor conducted Study 207, a 24-week, randomized, double-blind, active-controlled clinical trial in children ages 8-17 years with Type 2 diabetes mellitus, and a population pharmacokinetic study with sparse sampling technique in a subset of the population randomized to rosiglitazone.

After screening and a 4-week placebo run-in with diet counseling, patients were randomized to 2 mg twice daily of rosiglitazone (n=99) or to 500 mg twice daily of the control drug metformin (n=101), which had been approved for pediatric use. At 8 weeks, the dose of the medication was doubled in about half of both treatment groups based on fasting plasma glucose (FPG) concentration greater than 126 mg/dl.

The study protocol named the within-group change from baseline as the primary efficacy endpoint, and a non-inferiority comparison of change in HbA1c from baseline as the secondary efficacy comparison. The study was not adequately powered to rule out a difference in the HbA1c effects between the two treatments (favoring metformin) of 0.4% HbA1c units, defined prospectively as defining a clinically meaningful difference.

Initial inclusion criteria included patients who presented with HbA1c values between 7.1 and 10%, who were not adequately controlled on diet and exercise alone and who had not been treated pharmacologically for Type 2 diabetes mellitus, and who did not have type 1 diabetes mellitus, as demonstrated by stimulated c-peptide concentration > 1.5 ng/dl and negative GAD and 1CA512 autoantibodies. The sponsor lowered the HbA1c criterion to 6.5% as national diabetes guidelines with more intensive glycemic control were proposed and difficulties with enrollment were encountered. The screening HbA1c value was used as the randomization criterion. Thus 32 patients (16%) were randomized to pharmacologic treatment though the baseline HbA1c was less than 6.5%, a value below which pharmacologic treatment for Type 2 diabetes mellitus is usually not indicated. About one-half of the randomized patients (n=90) had been previously treated pharmacologically and had prior pharmacologic therapy for diabetes discontinued at screening.

The sponsor planned to screen 383 patients; 208 entered the run-in, and 200 were randomized at 59 centers in Canada (4), USA (33), Mexico (6), Brazil (3), Singapore (2), Hong Kong (2), Malaysia (3), Thailand (1), Hungary (1), Italy (1), Slovenia (1) , and the Netherlands (1). About 10% of the patients in each treatment group discontinued because of lack of efficacy, about 5% in each treatment group discontinued because of adverse events (and about half of these also demonstrated lack of efficacy), and 80 (81%) and 73 (72%) completed treatment with rosiglitazone and metformin, respectively. The randomized treatment groups were comparable at baseline in respect to mean age (14 years [age was reported in years, not months]), gender (2/3 were female) [the groups were stratified by gender], race (34% Hispanic, 28% Black, 22% white, 12% Asian, and 4% East Indian), weight (about 90 kg), body mass index (BMI) (33 kg/m^2), duration of diabetes (mean was 1 year) and prior diabetes therapy (55% diet only, monotherapy 38%, and combination therapy 8%). Most of the previously treated patients had taken metformin.

At baseline more of the patients in the metformin treatment group took additional medications (79% vs. 71%). The differences were most apparent in the following drug categories: nervous system (including analgesic and psychotropic medications: 27% vs. 16%, and 8% vs. 2%, respectively), respiratory system (27% vs. 13%), systemic hormonal therapy (including steroids and thyroid hormones; 7% vs. 3%). Even though most of the randomized patients met the adult World Health Organization (WHO) criterion for obesity (BMI > 30 kg/m^2), a history of obesity was listed only for about 18% of the patients. Sixteen percent of the patients had acanthosis nigricans. Family history, Tanner staging of puberty, menstrual history, and evaluation of height velocity standardized for age and gender were not included in the study report.

Efficacy

A summary of the sponsor's efficacy analyses for fasting plasma glucose and HbA1c of the total randomized population and the naïve subgroup is outlined in the table below. As

expected, fasting plasma glucose (FPG) decreased in patients naïve to diabetes medication (n=104) and increased in patients withdrawn from prior medication (usually metformin) (n=90) during the run-in period. The sponsor did not include efficacy data for the subgroup of randomized previously treated patients in the NDA submission. Since it takes about three months for the change in HbA1c, the primary efficacy variable, to reflect a steady state, the changes in glycemia from screening to baseline are better reflected in the secondary efficacy variable, FPG.

Summary Table of Efficacy at 24 Weeks (Intent to treat, LOCF**)**
for all randomized pediatric patients and subgroup of naïve patients.
Data Sources: Sponsor's tables 11, 12, 19, 20

	Randomized Patients		Naïve Patients	
	metformin	rosiglitazone	metformin	rosiglitazone
N	98	96	50	54
FPG (mg/dl)				
Screening (mean, SD)	160 (57)	156 (58)	157 (50)	158 (53)
Baseline (mean, SD)	183 (76)	169 (68)	158 (63)	156 (58)
Change from baseline (mean,SD)	-23 (61)	-6 (56)	-17 (56)	-7.6 (45)
95% CI	-35.1, -10.4	-17.1, 5.6	-33.1, -1.2	-19.9, 4.8
p-value	0.0004	0.3183	0.0352	0.2239
Treatment difference (rosiglitazone – metformin)		12		8
95% CI for the difference		-3.3, 27.0		-10.6, 26.9
p-value		0.1249		0.3931
% patients with ≥ 30 mg/dl decrease from baseline	36.7%	22.9%	34.0%	22.2%
N	98	97	50	55
HbA1c (%)				
Screening (mean, SD)	8.1 (1.3)	8.2 (1.4)	8.2 (1.4)	8.3 (1.5)
Baseline (mean, SD)	8.2 (1.6)	7.9 (1.5)	7.8 (1.6)	7.8 (1.4)
Change from baseline (mean,SD)	-0.49 (1.65)	-0.14 (1.52)	-0.60 (1.59)	-0.32 (1.64)
95%CI	-0.82,-0.16	-0.45, 0.17	-1.05, -0.15	0.76, 0.12
p-value	0.0043	0.3629	0.0104	0.1552
Treatment difference (rosiglitazone – metformin)		0.28		0.25
95% CI for the difference		-0.16, 0.72		-0.37, 0.87
p-value		0.2047		0.4309
% patients with ≥ 0.7% decrease from baseline	51.0%	36.1%	54.0%	43.6%

The FDA considered the non-inferiority comparison as primary, as within-group comparisons are not alone adequate to establish the extent of the effect attributable to drug. For the overall intent-to-treat population, at Week 24, the mean change from baseline in HbA1c was -0.14% with rosiglitazone and -0.49% with metformin, (95% CI for the difference, -0.16, 0.72). The upper bound of the confidence interval (0.72%) exceeded the proposed 0.4% change in HbA1c established as the criterion for inference

of non-inferiority of rosiglitazone to metformin. Therefore, there were insufficient patients in this study to establish statistically whether these observed mean treatment effects were similar or different. The data were similar for the treatment-naïve subgroup. In both analyses, the total randomized population and the naïve subgroup, the changes from baseline in FPG and HbA1c in the rosiglitazone-treated group were small and not statistically significant. Rosiglitazone activity appeared to be less than previously observed in adult clinical trials.

Additional analyses by the sponsor of evaluable patients and non-parametric analyses and additional analyses by the FDA statistician of the naïve subgroup with baseline HbA1c>6.5% (i.e., excluding about 16% of the randomized patient population) also did not establish that the effects of the two treatments were statistically comparable. The FDA statistician's descriptive analysis (based on mean data) suggested that in the small subset of patients with HbA1c $\leq$ 6.5% at baseline, there was no change in HbA1c from baseline at 24 weeks in the metformin group (n=16) and perhaps a slight worsening (i.e., increase in HbA1c) in the rosiglitazone group (n=20) . Note that there was no placebo control in this study. Both groups benefited (HbA1c decreased) if baseline HbA1c was > 6.5 and ≤ 10% (n=72 metformin, n=68 rosiglitazone). When baseline HbA1c > 10%, the metformin group (n=13) improved (HbA1c was lower at 24 weeks), while the rosiglitazone group (n=11) worsened (HbA1c was higher at 24 weeks). There was much variability in the high HbA1c baseline group, and the n was relatively small.

Safety

No deaths were reported. There was one serious adverse event reported in the rosiglitazone group listed as the preferred term "hyperglycemia", which was actually mild diabetic ketoacidosis (glucose 292 mg/dl, 2+ ketonuria) that required insulin rescue. Six serious adverse events were listed in the metformin group, including three that were listed under the preferred terms "drug ineffective," "diabetic ketoacidosis," and "diabetes mellitus inadequate control." Glucose concentrations were in the high 200's and 300's in these three patients, and all three required insulin rescue, though one of them was reported as completing the study. The other three preferred terms were suicidal ideation, status asthmaticus, and menorrhagia, and none of these three patients required insulin rescue. A total of 6 patients (6%) in the rosiglitazone group and 7 (7%) patients withdrew from the study because of an adverse event. In the rosiglitazone group, 5 of these had uncontrolled diabetes of whom 3 received insulin rescue. One patient presented with bronchitis and gastroenteritis, facial and hand edema, and rectal hemorrhage. In those discontinuing metformin due to an adverse event, two had hypoglycemia, one had diarrhea and nausea, two had uncontrolled diabetes and required insulin rescue, and two presented with slightly elevated baseline alanine aminotransferase that increased to about 3X ULN during the study.

Adverse events associated with rosiglitazone treatment in adults include weight gain, anemia, increases in lipid parameters, edema, congestive heart failure, and other

cardiovascular adverse events. Fatal hepatic events that were associated with troglitazone, another thiazolidinedione, and resulted in its withdrawal from the market, have been seen only rarely in association with rosiglitazone based on postmarketing reports.

Significantly more weight gain was seen for pediatric patients treated with rosiglitazone (mean +2.7 kg) than with metformin (mean –0.3 kg), a difference consistent with the known effects of these drugs in adults. About 54% of rosiglitazone-treated patients and 30% of metformin-treated patients gained 2 kg or more on study. About 1/3 of rosiglitazone-treated patients gained 5 kg or more, and none of the metformin-treated patients gained more than 5 kg. Of note, height was apparently not measured precisely in this study, as about 11% of the children had a height decrease of ≥ 1 cm, and about 40% had no change or a decrease at 24 weeks. Thus, analyses of changes in body mass index (perhaps more appropriate than weight for assessments of changes in adiposity related to rosiglitazone therapy in growing children) were not possible. Observed changes in hemoglobin were smaller than those observed in adult studies. Variability in the lipid measurements and the small sample size contributed to poor estimates of change in the lipids. Only one episode of edema was reported in the rosiglitazone treatment group, and there were no other adverse cardiovascular events reported, as expected in this young population. Gastrointestinal events were more commonly reported in the metformin treatment group (24% vs. 14%). There were two reports of transaminase elevation 3X the upper limit of normal in the metformin group, but none were reported in the rosiglitazone treatment group.

Hypoglycemia is rarely reported with either rosiglitazone or metformin. There were no reports of hypoglycemia with rosiglitazone and two with metformin. Diabetic ketoacidosis is rarely reported in adult studies of rosiglitazone and metformin. Five patients in the rosiglitazone treatment group and three patients in the metformin treatment group had mild diabetic ketoacidosis (serum glucose about 300 mg/dl, 2+ ketonuria) and/or required insulin rescue.

Overall Assessment

Only modest glucose lowering activity, likely inferior to metformin, was noted with rosiglitazone therapy in this pediatric study, counterbalanced by significant average weight gain relative to metformin. Because of this suboptimal risk-benefit ratio, rosiglitazone therapy is not indicated in the pediatric population. The pediatric efficacy and safety findings are summarized in the prescribing information.

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/s/

David Orloff

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