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APPLICATION NUMBER:

200678Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Addendum to the Clinical Pharmacology Review Dated October 15, 2010

NDA: 200678	Submission Date(s): 12/29/2009
Brand Name	Kombiglyze XR
Generic Name	saxagliptin/metformin HCl extended release fixed dose combination (FDC) tablets
Reviewer	Ritesh Jain, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology- II
OND division	Metabolism and Endocrinology Products
Sponsor	Bristol Myers Squibb
Submission Type; Code	Original NDA 505(b)(1); Standard
Formulation; Strength(s)	FDC product of saxagliptin/metformin XR at dose strengths 5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

BACKGROUND:

NDA 200678 was submitted to seek a marketing approval for Kombiglyze XR (FDC) 5 mg/500 mg, 2.5 mg/1000 mg, and 5 mg/1000 mg of saxagliptin/metformin hydrochloride extended-release tablets. The Clinical Pharmacology review for this NDA was DARRTed on October 15, 2010. In this review, under the Summary of Important Clinical Pharmacology Findings section, this reviewer mentioned that the proposed FDC product was not studied in the Phase 3 trials. Thus, pivotal BE studies provided the link between the formulations utilized in Phase 3 trials and the proposed to-be-marketed formulation. This addendum to Clinical Pharmacology review dated October 15, 2010 clarifies the link between the Kombiglyze XR and the formulations used in Phase 3 clinical trials. There were no long term clinical efficacy or safety studies conducted with either Kombiglyze XR or metformin hydrochloride XR co-administered with saxagliptin with this NDA. The following studies were submitted in support of this NDA:

- Long term Phase 3 safety and efficacy trials conducted (typically 24-52 week long) with metformin hydrochloride immediate-release formulation (Glucophage IR) co-administered with saxagliptin under NDA 22350.
- 4-week, multi-center, randomized, double-blind, placebo-controlled, Phase 3b trial (CV181066) conducted with metformin hydrochloride extended-release formulation (Glucophage XR) co-administered with saxagliptin under this NDA.
- Bioequivalence study, CV181111 and CV181112 comparing the rate and extent of absorption of saxagliptin and metformin hydrochloride when administered as Kombiglyze XR or saxagliptin and metformin hydrochloride XR tablets administered together.

The duration of 4-week trial (CV181066) mentioned above is not sufficient to evaluate the efficacy and safety of metformin hydrochloride extended-release formulation (Glucophage XR) co-administered with saxagliptin.

Reviewer's Findings on Pharmacokinetic Link between Glucophage IR vs. Glucophage XR:

Glucophage XR is approved under NDA 21202. In NDA 21202, the steady state pharmacokinetics of 4 doses of Glucophage XR was evaluated in study CV138-028. In this study, sixteen healthy volunteers were dosed with 500 mg Glucophage XR (referred as biphasic in Table 1) as single dose and PK samples were taken. Subjects then received nightly doses of 500 mg Glucophage XR for a week and PK samples were again obtained after a week of dosing. The 500 mg dose of Glucophage XR increments continued each week up to 2000 mg QD. In this study, subjects also received 2 x 500 mg BID Glucophage IR tablets for one week to provide comparative PK parameters between Glucophage XR and Glucophage IR. The results of the study are summarized in Table 1.

At steady state, the peak plasma concentrations for Glucophage XR (1000 mg QD biphasic) were approximately 20% lower compared to the same dose of Glucophage IR (1000 mg BID Glucophage). However, the extent of absorption of Glucophage XR (2000 mg QD biphasic, as measured by AUC) is similar to Glucophage IR (1000 mg BID Glucophage) (Table 1).

Table 1: Steady State Pharmacokinetics of Glucophage XR *

Treatment	N	Cmax (ng/ml)	Tmax$ (hr)	AUC (ng.hr/ml)*
500 mg biphasic single dose	16	645(115)	7(4,8)	6866(1751)
500 mg QD biphasic	16	603(166)	6(4,8)	6316(1996)
1000 mg QD biphasic	16	1080(259)	7(4,8)	12587(3164)
1500 mg QD biphasic	15	1441(362)	7(5,8)	16820(4160)
2000 mg QD biphasic	14	1780(288)	7(4,9)	20451(4114)
1000 mg BID Glucophage®	15	1321(234)	3(1.5,6)	20544(4445)

$ Median (range)
* AUC(INF) for 500 mg single dose; all others AUC(0-24).
CMAX and TMAX for the Glucophage® treatment are from the PM dose.

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***** ***Source: NDA 21202 review by Dr Robert M. Shore***

The formal PK comparison between the Glucophage XR 2000 mg QD and Glucophage IR 1000 mg BID is shown in Table 2. Results from the comparison demonstrated that the extent of absorption of Glucophage XR (as measured by AUC) is similar to that of Glucophage IR (Table 2).

Table 2: Pharmacokinetic Comparison of Glucophage XR 2000 mg QD and Glucophage IR 1000 mg BID*.

Parameter	Adjusted geometric means		Ratio of geometric means	
	2000 mg Biphasic QD	1000 mg Glucophage® BID	Point estimate	90% CI
CMAX (ng/ml)	1763	1297	1.36	(1.29, 1.44)
AUC(TAU) (ng.hr/ml)	19986	20053	1.00	(0.93, 1.07)

***** ***Source: NDA 21202 review by Dr Robert M. Shore***

Reviewer's Findings on Safety and Efficacy Link between Glucophage IR vs. Glucophage XR:

Phase 3 clinical trials in NDA 21202 demonstrated the safety and efficacy of Glucophage XR. The efficacy and safety of Glucophage XR was established in a 12-week, double-blind, randomized, placebo-controlled trial (CV138010) (Table 3).

Table 3: Change in HbA1C at week 12 and 24 week following administration of Glucophage XR*.

Change in HbA1c at 12 and 24 weeks (or last available measurement)

	12 weeks		24 weeks	
IHbA1c	Placebo n=79	Met XR n=155	Placebo n=79	Met XR n=156
Baseline	7.88	8.04	7.88	8.04
Week 12/24	8.00	7.47	8.09	7.42
Adj Mean chng	+0.09	-0.56	+0.19	-0.62
Diff		-0.65		-0.79

From table 11.1.1.4.1

* ***Source: NDA 21202 review by Dr Robert Misbin***

The results from another Phase 3 trial (Study 138036) under NDA 21202, a 16-week, double-blind, placebo-controlled, dose-response study of Glucophage XR, taken once daily with the evening meal or twice daily with meals, in patients with type 2 diabetes clearly demonstrated a dose response with increasing dose of Glucophage XR (Table 4).

Table 4: Summary of Mean Changes from Baseline in HbA1c, Fasting Plasma Glucose, and Body Weight at Final Visit (16 week study)*

	GLUCOPHAGE XR					Placebo
	500 mg Once Daily	1000 mg Once Daily	1500 mg Once Daily	2000 mg Once Daily	1000 mg Twice Daily	
Hemoglobin A_{1c} (%)	**(n=115)**	**(n=115)**	**(n=111)**	**(n=125)**	**(n=112)**	**(n=111)**
Baseline	8.2	8.4	8.3	8.4	8.4	8.4
Change at FINAL VISIT	-0.4	-0.6	-0.9	-0.8	-1.1	0.1
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	-
FPG (mg/dL)	**(n=126)**	**(n=118)**	**(n=120)**	**(n=132)**	**(n=122)**	**(n=113)**
Baseline	182.7	183.7	178.9	181.0	181.6	179.6
Change at FINAL VISIT	-15.2	-19.3	-28.5	-29.9	-33.6	7.6
p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	-
Body Weight (lbs)	**(n=125)**	**(n=119)**	**(n=117)**	**(n=131)**	**(n=119)**	**(n=113)**
Baseline	192.9	191.8	188.3	195.4	192.5	194.3
Change at FINAL VISIT	-1.3	-1.3	-0.7	-1.5	-2.2	-1.8
p-value[a]	NS**	NS**	NS**	NS**	NS**	-

* All patients on diet therapy at Baseline

[a] All comparisons versus Placebo

** Not statistically significant

* ***Source: Glucophage XR product label***

In NDA 21202, the sponsor had a Phase 3 trial (Study 138012) comparing metformin Glucophage IR to metformin Glucophage XR. The study was a double blind trial to compare two doses of Glucophage XR (1000 mg and 1500 mg) given once daily to Glucophage IR 500 mg BID in patients who had already been taking Glucophage IR 500 mg twice daily for at least 8 weeks. The results from the trial are shown in Table 5.

Table 5: Summary of Mean Changes from Baseline* in HbA1c, Fasting Plasma Glucose, and Body Weight at Week 12 and at Final Visit (24-week study) ‡

	GLUCOPHAGE 500 mg Twice Daily	GLUCOPHAGE XR	
		1000 mg Once Daily	1500 mg Once Daily
Hemoglobin A_{1c} (%)	**(n=67)**	**(n=72)**	**(n=66)**
Baseline	7.06	6.99	7.02
Change at 12 Weeks	0.14	0.23	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at FINAL VISIT	0.14[a]	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
FPG (mg/dL)	**(n=69)**	**(n=72)**	**(n=70)**
Baseline	127.2	131.0	131.4
Change at 12 Weeks	12.9	9.5	3.7
(95% CI)	(6.5, 19.4)	(4.4, 14.6)	(-0.4, 7.8)
Change at FINAL VISIT	14.0	11.5	7.6
(95% CI)	(7.0, 21.0)	(4.4, 18.6)	(1.0, 14.2)
Body Weight (lbs)	**(n=71)**	**(n=74)**	**(n=71)**
Baseline	210.3	202.8	192.7
Change at 12 Weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at FINAL VISIT	0.9	1.1	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

* All patients on GLUCOPHAGE 500 mg twice daily at Baseline

[a] n=68

‡ ***Source: Glucophage XR product label***

Thus, NDA 21202 demonstrated the comparable bioavailability between Glucophage XR and Glucophage IR. The differences in C_{max} between the two formulations did not appear to result marked differences in efficacy based on a clinical trial in which patients with T2DM receiving Glucophage IR were either maintained on this regimen or switched to Glucophage XR.

Reviewer's Findings on pivotal BE studies CV181111 and CV181112 submitted under NDA 200678:

Bioequivalence trials, CV181111 and CV181112, comparing Kombiglyze XR to the individual components metformin hydrochloride XR and saxagliptin co-administered together demonstrated that there is no formulation effect.

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