CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-350

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-350	*Submission Date(s)*	6/30/08, 10/24/08, 11/19/08, 11/24/08, 12/2/08, 1/26/09
Brand Name		Onglyza	
Generic Name		Saxagliptin; BMS-477118	
Reviewers		Jayabharathi Vaidyanathan, Ph.D. Immo Zdrojewski, Ph.D.	
Team Leader (Acting)		Wei Qiu, Ph.D.	
PM Reviewer		Justin Earp, Ph.D.	
PM Team Leader		Christoffer Tornoe, Ph.D.	
OCP Division		Division of Clinical Pharmacology-2	
OND Division		Division of Metabolic and Endocrine Products	
Sponsor		Bristol-Myers Squibb	
Relevant IND(s)		63,634	
Submission Type; Code		Original 505 (b) (1) NME	S
Formulation; Strength(s)		Immediate release tablets; 2.5 mg and 5 mg	
Indication		Treatment of Type 2 diabetes	

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1 Executive Summary

Saxagliptin belongs to the DPP-4 inhibitor class of anti-diabetic agents. Januvia (sitagliptin) is the first approved DPP-4 inhibitor (NDA 21-995; approval date, Oct 16, 2006) by the FDA and the Agency

b(4)

Saxagliptin is intended to improve glycemic control for patients with type 2 diabetes mellitus (T2DM). Sponsor is proposing saxagliptin as monotherapy, as an adjunct to diet and exercise; in combination with metformin, a thiazolidinedione (TZD), or a sulfonylurea (SU) when the single agent alone, with diet and exercise does not provide adequate glycemic control; and also as initial combination with metformin, as an adjunct to diet and exercise, when treatment with dual saxagliptin and metformin therapy is appropriate.

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 22-350 for Onglyza (saxagliptin) and finds it acceptable provided that the Agency and the sponsor agree on the labeling. The recommendation and the following comments should be sent to the sponsor as appropriate.

- It is recommended to reduce the dose to 2.5 mg when co-administered with strong CYP3A4/5 inhibitors.
- Labeling comments on page 47.

Required office level OCP briefing was held on Thursday, March 26 2009 and the attendees were Drs. Chandra Sahajwalla, Suresh Doddapaneni, Wei Qiu, Hylton Joffe, Naomi Lowy, Fred Alavi, Todd Bourcier, Joga Gobburu, Mehul Mehta, Atik Rahman, Gil Burckhart, Kellie Reynolds, Sally Choe, Jayabharathi Vaidyanathan, Justin Earp, Michael Pacanowski, Johnny Lau, Sang Chung, Ritesh Jain, Immo Zdrojewski and Yun Xu.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The clinical pharmacology of saxagliptin has been characterized in 27 studies in healthy volunteers and T2DM patients. In addition, there are 23 bioanalytical study reports, 17 *in*

vitro metabolism/permeability studies, and one protein binding study. Based on these studies, saxagliptin demonstrates the following properties:

Pharmacokinetic/ Biopharmaceutics Properties

- Single dose and multiple dose pharmacokinetics of saxagliptin were similar and there was no accumulation after once-daily dosing for 14 days. Following repeated administration, steady-state trough levels on day 2 was similar to that on day 4. The median Tmax was between 1.5-2.0 h following the 2.5 and 5 mg dose. **The elimination half-life in patients was 2.3 – 3.3 h. The pharmacokinetics** of saxagliptin in T2DM patients was similar to that observed in healthy subjects. Overall the AUC and Cmax increased proportionally with dose in the dose range of 2.5 mg to 50 mg in T2DM patients and 40 mg to 400 mg in healthy volunteers. The following Tables 1 and 2 present the PK parameters of saxagliptin in healthy subjects and T2DM patients, respectively.

Table 1: Summary statistics of saxagliptin PK parameters in healthy subjects (Study 010)

Saxagliptin PK Parameter	Saxagliptin Dose	Study Day	
		Day 1 n=10 for 40 mg n=6 for all other doses	Day 14 n=10 for 40 mg n=6 for all other doses [a]
Cmax (ng/mL) Geometric Mean (C.V. %)	40 mg	226 (40)	224 (33)
	100 mg	585 (19)	487 (14)
	150 mg	694 (25)	614 (19)
	200 mg	1207 (11)	985 (22)
	300 mg	1845 (20)	1630 (31)
	400 mg	2321 (18)	1863 (22)
AUC(TAU) (ng·h/mL) Geometric Mean (C.V. %)	40 mg	739 (26)	800 (24)
	100 mg	1899 (18)	1998 (11)
	150 mg	2543 (11)	2532 (9)
	200 mg	4186 (15)	4090 (10)
	300 mg	6652 (22)	6539 (26)
	400 mg	8364 (14)	8532 (13)
A.I. for AUC(TAU) Geometric Mean (C.V. %)	40 mg	N/A	1.08 (18)
	100 mg		1.05 (15)
	150 mg		1.00 (13)
	200 mg		0.99 (19)
	300 mg		0.98 (14)
	400 mg		1.02 (8)
Tmax (h) Median (Min, Max)	40 mg	1.00 (0.75, 2.00)	0.88 (0.50, 2.00)
	100 mg	1.13 (0.50, 2.00)	1.50 (1.50, 2.00)
	150 mg	1.50 (0.50, 2.00)	1.25 (0.75, 2.00)
	200 mg	1.50 (0.50, 2.00)	1.50 (0.75, 2.00)
	300 mg	1.50 (1.00, 1.50)	1.75 (1.00, 2.00)
	400 mg	1.50 (1.00, 1.50)	1.50 (0.75, 2.00)
T-HALF (h) Mean (S.D.)	40 mg	2.29 (0.18)	2.46 (0.29)
	100 mg	2.32 (0.22)	3.03 (1.29)
	150 mg	2.27 (0.14)	2.69 (0.91)
	200 mg	2.25 (0.21)	3.58 (1.25)
	300 mg	2.88 (0.85)	5.38 (3.44)
	400 mg	3.79 (1.11)	5.48 (2.55)
%UR Mean (S.D.)	40 mg	26 (6)	25 (10)
	100 mg	19 (5)	23 (8)
	150 mg	18 (5)	22 (8)
	200 mg	24 (9)	29 (6)
	300 mg	25 (3)	26 (8)
	400 mg	27 (10)	20 (10)

CLR (mL/min) Mean (S.D.)	40 mg	259 (77)	220 (78)
	100 mg	183 (56)	221 (90)
	150 mg	189 (54)	230 (82)
	200 mg	199 (69)	241 (36)
	300 mg	191 (68)	196 (37)
	400 mg	213 (80)	159 (91)

Table 2: Summary statistics of saxagliptin PK parameters in T2DM patients (Study 002)

Pharmacokinetic Parameter	BMS-477118 Dose	Study Day		
		Day 1 (n=6)	Day 7 (n=6)	Day 14 (n=6)
Cmax (ng/mL) Geometric Mean (C.V. %)	2.5 mg	11 (34)	11 (27)	12 (23)
	5 mg	21 [a] (18)	23 (31)	25 (22)
	15 mg	94 (26)	87 (14)	89 (20)
	30 mg	122 (33)	141 (34)	141 [b] (25)
	50 mg	206 (11)	211 (24)	218 (13)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	2.5 mg	33 (28)	34 (20)	34 (20)
	5 mg	77 [a] (25)	76 (18)	81 (20)
	15 mg	371 (19)	375 (18)	365 (25)
	30 mg	618 (40)	682 (42)	676 (38)
	50 mg	949 (17)	917 (14)	915 [b] (19)
A.I. for AUC(0-T) Geometric Mean (C.V. %)	2.5 mg		1.05 (16)	1.05 (12)
	5 mg		1.00 [a] (9)	1.06 [a] (5)
	15 mg		1.01 (5)	0.99 (15)
	30 mg		1.10 (7)	1.09 [b] (9)
	50 mg		0.97 (8)	1.04 [b] (2)
Tmax (h) Median (Min, Max)	2.5 mg	1.50 (0.75, 2.00)	1.25 (1.00, 4.00)	1.50 (0.75, 2.00)
	5 mg	2.00 [a] (1.00, 3.00)	2.50 (1.50, 3.00)	2.00 (1.50, 4.00)
	15 mg	2.00 (0.75, 3.00)	2.00 (1.50, 2.00)	1.75 (1.00, 2.00)
	30 mg	3.00 (2.00, 4.00)	2.00 (2.00, 3.00)	2.00 (1.00, 3.00)
	50 mg	2.50 (1.00, 3.00)	1.50 (1.50, 3.00)	1.50 [b] (1.50, 3.00)
T-HALF (h) Mean (S.D.)	2.5 mg	3.84 (1.72)	3.67 [a] (1.43)	3.32 (1.11)
	5 mg	2.21 [a] (0.15)	2.35 (0.48)	2.33 [a] (0.24)
	15 mg	2.46 (0.50)	2.48 (0.40)	2.55 (0.35)
	30 mg	2.35 (0.40)	2.33 (0.30)	2.36 (0.35)
	50 mg	2.17 (0.27)	2.39 (0.34)	2.27 [b] (0.20)
%UR Mean (S.D.)	2.5 mg	14 (7)	14 (3)	12 (4)
	5 mg	12 [a] (7)	22 [a] (7)	13 (5)
	15 mg	22 (4)	21 (5)	22 (5)
	30 mg	25 (6)	24 (4)	25 (3)
	50 mg	18 (4)	14 (7)	12 [b] (5)
CLR (mL/min) Mean (S.D.)	2.5 mg	–	–	–
	5 mg	–	–	–
	15 mg	140 [c] (50)	149 [c] (47)	123 [b] (33)
	30 mg	196 [a] (57)	163 [a] (36)	175 [a] (40)
	50 mg	157 [a] (35)	124 (69)	116 [b] (70)

- The mean exposure of the major active metabolite, BMS-510849 was 1.7 - 3 fold and 4-7 fold higher than the parent in healthy subjects and T2DM patients, respectively. The molar ratio of BMS-510849 to saxagliptin was similar on Days 1, 7 and 14 within each dose. The median Tmax was 3 h and the mean apparent terminal half-life was 3.6 h following 5 mg dose.
- Co-administration of a 10 mg tablet with a high fat meal resulted in a 27% increase in AUC of saxagliptin and a decrease in exposure of BMS-510849 (Cmax decreased by 18%). The median Tmax of saxagliptin was prolonged from 0.53 h to 0.99 h, while the median Tmax of BMS-510849 increased from 1.47 h to 1.98 h when saxagliptin was administered following a high-fat meal. The sponsor is requesting biowaiver for conducting additional clinical food effect

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