# PharmaNote®

Volume 25, Issue 5 February 2010


## SAXAGLIPTIN: A NEW "GLIPTIN" APPROVED FOR TYPE II DIABETES

Johanna Kaharl, Pharm.D. Candidate

Saxagliptin was approved by the FDA July 31, 2009 under the brand name Onglyza®.[1] This agent is a new dipeptidyl peptidase 4 inhibitor (DPP-4 inhibitor), similar to Sitagliptin (Januvia®). Manufactured by Bristol Myers Squibb, saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with Type II Diabetes Mellitus (DM) and has been studied in combination with other oral diabetic medications.[2] The aim of this article is to give a general overview of saxagliptin, including its pharmacokinetics, efficacy as a monotherapy and in combination with other diabetic medications, and adverse effects.

### PHARMACOLOGY

Saxagliptin inhibits DPP-4 mediated metabolism of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are normally excreted by the small intestine in response to meals and then inactivated by DPP-4 within minutes.[3] The incretins stimulate the beta cells of the pancreas to release insulin in a glucose-dependent manner, lower glucagon secretion from the alpha cells, and slow gastric emptying.[4] Saxagliptin causes a 2- to 3-fold increase in circulating GLP-1 and GIP levels, leading to decreased glucagon concentrations and increased glucose-dependent insulin secretion.[2] In pre-clinical trials, incretin agents like the DPP-4 inhibitors and the GLP-1 receptor agonist exenatide (Byetta®) have been associated with an increased pancreatic beta-cell mass.[4] Future clinical studies are needed to assess their full effect on reversing pancreatic beta-cell dysfunction.

### PHARMACOKINETICS

Saxagliptin's major metabolite is 5-hydroxy saxagliptin. This active metabolite has 50% of the potency of saxagliptin and a similar pharmacokinetic profile (Table 1).

### SPECIAL POPULATIONS

*Renal Impairment*

In a single-dose, open-label study, the pharmacokinetics of saxagliptin in subjects with varying degrees of chronic renal impairment (N=8 per group) were compared to subjects with normal renal function. The area-under-the-curve (AUC) was 2.1 and 4.5 fold higher in saxagliptin and 5-hydroxysaxagliptin in subjects with moderate to severe renal impairment (CrCl of ≤ 50ml/min) versus subjects with normal renal function. Therefore, a lower dose of 2.5mg daily is recommended in patients with CrCl ≤ 50ml/min. As saxagliptin is removed by hemodialysis, these patients

INSIDE THIS ISSUE:

**Table 1. Pharmacokinetics of saxagliptin.[2]**

| | |
|---|---|
| **ABSORPTION** | Tmax: 2 hours for saxagliptin; 4 hours for 5-hydroxy saxagliptin |
| **DISTRIBUTION** | No protein binding shown *in vitro* |
| **METABOLISM** | Hepatic through CYP3A4/5 (to less potent metabolite) |
| **EXCRETION** | Renal:<br>• Median saxagliptin clearance was higher than glomerular filtration suggesting active tubular excretion<br>• Following a single 50mg dose of 14C-saxagliptin, the following were recovered in urine: 24% as saxagliptin and 36% as metabolite<br>• Saxagliptin is removed by hemodialysis (23% of dose over 4 hours)<br>Fecal:<br>• 22% was recovered in feces representing drug excreted in bile and/or not absorbed from GI tract<br>• Mean Terminal $t_{1/2}$: 2.5 h |

**Tmax** = time to maximal concentration; **CYP** = Cytochrome P450 enzymes; **GI** = Gastrointestinal; **$t_{1/2}$** = half-life

should take their doses after dialysis sessions.[2]

*Hepatic Impairment*

No dose adjustment is recommended for patients with hepatic impairment owing to a lack of any clinically significant impact on AUC.[2]

*Geriatric Patients*

Roughly 15% of diabetic subjects in phase III trials were above age 65. No differences were noted in safety and efficacy for those greater than 65 years when compared with younger subjects.

*Pregnancy*

Saxagliptin is designated as category B as it was not teratogenic in animal studies, but no adequate, well-controlled studies have been performed in pregnant women.[2]

## DRUG INTERACTIONS

Saxagliptin is a substrate of CYP3A4/5 enzymes, but *in vitro* studies showed no inhibition or inducement of any CYP enzyme subfamilies. Saxagliptin is also a substrate of P-glycoprotein (PGP), but causes no significant interaction in PGP binding. Furthermore, saxagliptin undergoes no significant protein binding. In vivo studies showed no significant saxagliptin-induced effect on AUC of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole.

Drugs known to affect the metabolism of saxagliptin are summarized in Table 2.

## EFFICACY

*Monotherapy*

The efficacy and safety of saxagliptin as monotherapy was evaluated in a phase III, 24 week, four-arm, parallel-group, double blind, randomized, placebo-controlled trial (RCT).[5] The main treatment cohort (MTC) inclusion criteria required that patients be between the ages of 18 and 77 with type 2 diabetes inadequately controlled (which the study defined as $A_{1c}$ ≥ 7.0% and ≤ 10%) with diet and exercise. Patients were required to be treatment naïve, defined as not

**Table 2. Effects of other drugs on saxagliptin.[2]**

| | |
|---|---|
| **CYP3A4 INDUCERS** | • Rifampin ↓ AUC of saxagliptin but not 5-hydroxy saxagliptin. No effect on the activity of saxagliptin at the DPP4 enzyme.<br>• No dose adjustment is recommended |
| **CYP3A4 INHIBITORS** | |
| *Moderate Inhibitors* | • Diltiazem ↑ AUC of saxagliptin 2-fold, causing a decrease in the AUC of 5-hydroxy saxagliptin.<br>• No dose adjustment is recommended |
| *Strong Inhibitors* | • Ketoconazole ↑AUC of saxagliptin from 2.5-3.7 fold with a subsequent ↓ in 5-hydroxy saxagliptin.<br>• A lower dose of saxagliptin 2.5mg daily is recommended if concurrent therapy with strong inhibitors such as ketoconazole, itraconazole, clarithromycin, and protease inhibitors. |

having received insulin or oral antihyperglycemic medication for at least 6 months since diagnosis. Exclusion criteria included symptoms of poorly controlled diabetes, history of diabetic ketoacidosis, or any significant comorbidities such as a CV event with 6 months, NYHA stage III/IV CHF, morbid obesity, renal or liver impairment. After a 2 week, single blind, diet, exercise, and placebo lead-in period, the 401 subjects in the MTC were randomized to saxagliptin 2.5 mg daily, 5 mg daily, 10 mg daily, or placebo. Patients with a $A_{1c}$ > 10% and ≤ 12%, but who met all other inclusion/exclusion criteria were eligible to enroll in an open-label cohort (OLC) with saxagliptin 10mg daily. All patients who were deemed to have inadequate glucose control during the study based on fasting plasma glucose levels were eligible for addition of open-label metformin as rescue therapy. In rescue patients, efficacy was evaluated as the last value measured before rescue therapy. Rescue therapy was required in 15% of the 2.5 mg group, 20% of the 5mg group, 14% in the 10mg group, and 26% of the placebo group. The primary endpoint was $A_{1c}$ adjusted mean change from baseline using last observation carried forward (LOCF) at week 24. At week 24, saxagliptin 2.5 and 5 mg caused statistically significant reductions in $A_{1c}$ ($p < 0.0001$) and FPG ($p < 0.05$) from baseline versus those randomized to placebo (Table 3).[5]

*Combination therapy*

Coadministration of saxagliptin with metformin in treatment naïve patients was evaluated in a phase III, 24 week, double-blind, randomized controlled trial (RCT) of diabetic patients with the primary outcome measured as reduction in $A_{1c}$ from baseline at 24 weeks.[6] Secondary endpoints included change from baseline at 24 weeks of FPG and postprandial glucose area-under-the-curve (PPG-AUC). Besides having inadequate glycemic control, defined as $A_{1c}$ ≥ 8% and ≤ 12%, inclusion/exclusion criteria were the same as those defined in the monotherapy trial. After a single blind, 1 week dietary and exercise lead-in period, 1306 subjects were randomized to 1 of 4 treatment arms: saxagliptin 5 mg daily plus metformin 500 mg daily, saxagliptin 10 mg daily plus metformin 500 mg daily, saxagliptin 10 mg plus placebo, or metformin 500mg plus placebo. The metformin dose could be uptitrated weekly in 500mg increments as tolerated to max of 2g daily over the first 5 weeks. Subjects who failed to meet specific glycemic goals were treated with pioglitazone as rescue add-on therapy. At week 24, patients randomized to saxagliptin 5 and 10 mg plus metformin demonstrated statistically significant reductions in $A_{1c}$ ($p < 0.0001$), FPG ($p < 0.05$) and PPG-AUC ($p < 0.0001$) from baseline versus both monotherapy groups (Table 3).[6]

Addition of saxagliptin to metformin was evaluated in a phase III, 24 week, double blind RCT of 743 patients.[7] Patients had to have been on at least 8 weeks of metformin at a stable dose of 1500-2500 mg per day with inadequate glycemic control defined as $A_{1c}$ ≥ 7% and < 10%. All other inclusion/exclusion criteria were similar to previously mentioned trials. After a single blind, 2 week dietary and exercise lead in period with patients receiving pre-study doses of metformin, patients were randomized to add on 2.5 mg saxagliptin daily, 5 mg saxagliptin daily, 10 mg saxagliptin daily, or placebo. The primary endpoint was $A_{1c}$ change from baseline and secondary endpoints included FPG and PPG-AUC. Patients who failed to meet glycemic goals were treated with pioglitazone rescue therapy. At week 24, saxagliptin added to metformin was well tolerated with statistically significant improvement in $A_{1c}$ ($p < 0.0001$), FPG ($p < 0.0001$), and PPG-AUC ($p < 0.0001$) versus placebo added to metformin.[7]

Addition of saxagliptin to thiazolidinedione (TZD) was evaluated in a phase III, 24 week, double blind RCT with 565 patients.[8] Patients had to have been on a stable dose of either pioglitazone 30 to 45 mg daily or rosiglitazone 4 mg once to twice daily or 8 mg daily with inadequate glycemic control defined as $A_{1c}$ ≥ 7% and < 10%. All other inclusion/exclusion criteria match those of previously discussed trials. After a single blind, 2 week dietary and exercise lead in period with patients receiving pre-study doses of TZD, patients were randomized to add on saxagliptin 2.5 mg daily, 5 mg daily, or placebo with no dose titration of either medication. Change from rosiglitazone to pioglitazone at equivalent doses was permitted if deemed medically appropriate by the study investigator. Patients who failed to meet specified glycemic goals were treated with metformin as rescue therapy. Rescue occurred in 10% of the saxagliptin 2.5 mg group, 6% of the 5 mg group, and 10% of the placebo group. At week 24, saxagliptin 2.5 and 5 mg added to TZD had statistically significant greater reductions in $A_{1c}$ ($p < 0.05$) and FPG ($p <0.05$) versus placebo added to TZD.[8]

Addition of saxagliptin to a sulfonylurea was evaluated in a 24 week, double blind RCT of 768 patients.[9] Patients had to have been on a sub maximal dose of a sulfonylurea for at least 2 months prior to enrolling in the study with inadequate glycemic control, defined as $A_{1c}$ ≥ 7% and < 10%. All other inclusion/exclusion criteria match those of the trials previously discussed. During the 4 week, single blind, dietary and exercise lead-in period patients discontinued previous sulfonylurea and started receiving open-label glyburide 7.5 mg daily. Patients with $A_{1c}$ ≥ 7% and FPG

**Table 3. Summary of saxagliptin trial results.[5-9]**

| Therapy | N | Mean baseline $A_{1c}$ (%) | $A_{1c}$ Change (adjusted mean[B]) | FPG Change (mg/dL) | PPG-AUC Change[C] (mg·min/dL) | Percent Achieving $A_{1c}$ <7% | Percent on Rescue |
|---|---|---|---|---|---|---|---|
| **Monotherapy[5]** | | | | | | | |
| 2.5 mg daily | 100 | 7.9 | - 0.4 | -15 | -6868 | 35 | 15 |
| 5 mg daily | 103 | 8.0 | - 0.5 | -9 | -6896 | 38 | 20 |
| 10 mg daily | 95 | 7.9 | - 0.5 | -17 | -8084 | 41 | 14 |
| Placebo | 92 | 7.9 | + 0.2 | +6 | -647 | 24 | 26 |
| OLC | 64 | 10.7 | - 1.9 | -33 | -11078 | 14 | |
| | | | | | | | |
| **Combination Therapy** | | | | | | | |
| *Coadministration with metformin[6] in treatment naïve* | | | | | | | |
| Saxagliptin 5 mg + metformin | 320 | 9.4 | -2.5 | -60 | -21080 | 60 | 7.5 |
| Saxagliptin 10 mg + metformin | 323 | 9.5 | -2.5 | -62 | -21336 | 60 | 5.9 |
| Placebo + saxagliptin 10 mg | 335 | 9.6 | -1.7 | -31 | -16054 | 32 | 21.2 |
| Placebo + metformin | 328 | 9.4 | -2.0 | -47 | -15005 | 41 | 10.1 |
| | | | | | | | |
| *Add-on to metformin[7]* | | | | | | | |
| 2.5 mg daily | 192 | 8.1 | -0.6 | -14 | -8891 | 37 | ND |
| 5 mg daily | 191 | 8.1 | -0.7 | -22 | -9586 | 44 | ND |
| 10 mg daily | 181 | | -0.6 | -21 | -8137 | 44 | ND |
| Placebo | 179 | 8.1 | +0.1 | +1 | -3291 | 17 | ND |
| | | | | | | | |
| *Add-on to TZD[8]* | | | | | | | |
| 2.5 mg daily | 195 | 8.3 | -0.7 | ND | ND | 42 | ND |
| 5 mg daily | 186 | 8.4 | -0.9 | ND | ND | 42 | ND |
| Placebo | 184 | 8.2 | -0.3 | ND | ND | 26 | ND |
| | | | | | | | |
| *Add-on to glyburide[9]* | | | | | | | |
| 2.5 mg | 248 | 8.4 | -0.5 | -7 | -4296 | 22 | 18 |
| 5 mg | 253 | 8.5 | -0.6 | -10 | -5000 | 23 | 17 |
| Placebo + Up-titrated glyburide | 267 | 8.4 | +0.1 | +1 | +1196 | 9 | 30 |

[a] Mean change from baseline, using last observation carried forward at study end.
[b] Least squares mean adjusted for baseline value.
[c] Comparison or oral glucose tolerance test results from baseline to week 24.
**FPG =** fasting plasma glucose; **ND** = No Data, only abstract could be viewed; **OLC** = open-label cohort; **PPG-AUC** = post-prandial glucose area under the curve

≥ 140 mg/dL continued treatment with glyburide 7.5 mg daily and were randomized to add-on saxagliptin 2.5 mg daily, saxagliptin 5 mg daily, or placebo plus blinded glyburide 2.5 mg daily (uptitrated to initial total daily dose of glyburide 10 mg). Patients in placebo plus blinded glyburide were eligible to up-titrate the glyburide dose to 15 mg daily. However, glyburide could be down-titrated in all three groups for hypoglycemia when deemed necessary by investigator. The primary study endpoint was change in $A_{1c}$ from baseline to 24 weeks and secondary endpoints included changes in FPG and PPG-AUC. Those who failed to meet glycemic goals were treated with metformin rescue. Rescue or discontinuation due to lack of glycemic control occurred in 18% of the saxagliptin 2.5 mg add-on group, 17% of the 5 mg group, and 30% of the placebo plus up-titrated glyburide group. At week 24, saxagliptin 2.5 and 5 mg daily added to a sulfonylurea caused significantly greater reductions in $A_{1c}$ ($p < 0.0001$), FPG ($p = 0.002$), and PPG-AUC ($p < 0.0001$) versus placebo added to sulfonylurea (Table 3).[9]

No studies have assessed saxagliptin in combination with insulin.

**Table 4. Commonly reported adverse reactions in saxagliptin clinical trials.[2]**

| ADVERSE EFFECT | SAXAGLIPTIN 5 MG (%) | PLACEBO (%) |
|---|---|---|
| Upper respiratory tract infection | 7.7 | 7.6 |
| Urinary tract infection | 6.8 | 6.1 |
| Headache | 6.5 | 5.9 |
| Sinusitis | 2.6 | 1.6 |
| Abdominal Pain | 1.7 | 0.5 |
| Gastroenteritis | 2.3 | 0.9 |
| Vomiting | 2.3 | 1.3 |
| Hypersensitivity-related event (urticaria or facial swelling) | 1.5 | 0.4 |

[2]As summarized by manufacturer in package insert- pooled data from the 5 RCTs including monotherapy trials and add-on to metformin, TZD, and glyburide.

## ADVERSE DRUG REACTIONS

Due to adverse cardiovascular effects of rosiglitazone, the FDA now requires specific studies to prove a new diabetic medication has no effect on cardiac conduction. In a double-blind, 4-way crossover, active comparator RCT using moxifloxacin in 40 healthy subjects, saxagliptin did not cause a clinically meaningful prolongation of the QTc interval or effect the heart rate at daily doses up to 40 mg.[2] The FDA also requires post-marketing studies to assess possible adverse effects on patients with comorbid cardiac conditions, as phase III trials exclude patients with major comorbidities.

From a pooled analysis of five Phase III RCT's, a mean decrease of 100 and 120 cells/mcL relative to placebo was seen after 24 weeks of therapy with saxagliptin 5mg and 10mg respectively. The mean absolute lymphocyte count at baseline was 2200 cells/mcL. These decreases were seen in some patients upon rechallenge. The decrease in absolute lymphocyte count did not cause any clinically significant problems, but may need to be considered in patients with prolonged infection.

Hypoglycemia was reported more often when saxagliptin 5 mg was added to glyburide versus glyburide monotherapy (14.6% versus 10.1%). However, confirmed incidence of hypoglycemia (defined as symptoms of hypoglycemia and fingerstick glucose of ≤ 50 mg/dL) was similar in saxagliptin add-on and glyburide only groups (0.8% and 0.7% respectively). The incidence of hypoglycemia in other RCT's including saxagliptin as monotherapy and in combination with metformin or TZD was similar in treatment and placebo groups.[2]

Saxagliptin generally has no effect on weight.[10] Other commonly reported adverse reactions to saxagliptin are summarized in Table 4.

## DOSING

Saxagliptin is dosed at 2.5 mg or 5 mg PO once daily. The lower dose of saxagliptin 2.5 mg daily is preferred in patients with a CrCl of < 50 ml/min or in patients who are concurrently on a strong CYP3A4/5 inhibitor such as ketoconazole. Saxagliptin is not approved for use in children under the age of 18 as there have been no studies in pediatric patients.

## DOSING

The average monthly retail cost of Onglyza® 2.5 mg is $217.22 ($212.99-$223.68), and of Onglyza® 5 mg is $219.55 ($214.99-$223.68).

## SUMMARY

Saxagliptin is a DPP-4 inhibitor with many similarities to the other commercially available DPP-4 inhibitor, sitagliptin, including once daily administration, good tolerability and no evidence of cardiac toxicity in diabetic patients without comorbidities. Saxagliptin is effective in lowering $A_{1c}$ as monotherapy and can cause additional lowering of $A_{1c}$ in patients with uncontrolled diabetes when added to TZDs, sulfonylureas, and when added to or started with metformin.

♦ ♦ ♦

## REFERENCES

1. FDA Approves New Drug Treatment for Type 2 Diabetes. FDA News Release. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/

ucm174780.htm Page last updated 7/31/2009.
2. Onglyza® Package Insert. Last revised 7/2009.
3. Deacon CF, Holst JJ. Saxagliptin: a new dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes. Adv Ther 2009;26(5):488-99.
4. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-705.
5. Rosenstock J, Aguilar-Salinas C, Klein E, et al. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Research and Opinion 2009;25:10:2401-11.
6. Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R for the CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab 2009;11(6):611-22.
7. Defronzo RA, Hissa MN, Garber AJ, et al for the Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care 2009;32:1649-55.
8. Hollander P, Allen E, Li J, Chen R. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with inadequately controlled type 2 diabetes [abstract]. Diabetologia 2008;51(suppl 1.):S342.
9. Chacra AR, Tan GH, Apanovitch A, et al for the CV181-040 Investigators. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomized controlled trial. Int J Clin Pract 2009;63 (9):1395-1406.
10. Dhillon S, Weber J. Adis Drug Profile: Saxagliptin. Drugs 2009;69(15)2103-14.
11. Ahren B. Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin—diabetes control and potential adverse events. Best Pract Res Clin Endocrinol Metab 2009;23(4):487-98.

♦ ♦ ♦

## *Did you know?*

*PharmaNote® is also available electronically!*

If you'd prefer to receive PharmaNote monthly via...

***E-mail***: Please send an email with your name and e-mail address to the *Assistant Editor* (ssmithm@ufl.edu) and we would be happy to add you to the distribution list. All e-mail addresses are kept confidential.

***Web:*** PharmaNotes from 2002-present are available free of charge from the UF College of Pharmacy:

http://www.cop.ufl.edu/safezone/doty/pep/pharmanote/index.htm

***The PharmaNote is Published by:***
**The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research**
**University of Florida**