P&T®

PRODUCT PROFILER

Onglyza™

(saxagliptin) Tablets

FDA-approved indication

Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Important limitations of use:

- **Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis**
- **Has not been studied in combination with insulin**

Contents

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The Product Profiler

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PRODUCT PROFILER

Onglyza™

(saxagliptin) Tablets

Indication and Important Limitations of Use for ONGLYZA

ONGLYZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

ONGLYZA has not been studied in combination with insulin.

Please see US Full Prescribing Information on page 15.

ONGLYZA (saxagliptin) tablets

A dipeptidyl peptidase-4 inhibitor for adults with type 2 diabetes

INTRODUCTION

Type 2 diabetes is a serious, common, and costly disease, and is quickly becoming a national epidemic, affecting an estimated 23.5 million Americans aged 20 years or older (10.7% of this population)[1]. Of the entire US population (all ages), 17.9 million are diagnosed, and 5.7 million are undiagnosed[1]. The total diabetes burden is expected to reach 13.5% of the population (32.6 million) in 2021 and 14.5% of the population (37.7 million) by 2031[2].

There is significant unmet need in type 2 diabetes, illustrated by the fact that a large proportion of the adult type 2 diabetic population in the United States has uncontrolled (>7%) hemoglobin A1c (A1C)[3]. Nearly half of adult patients with type 2 diabetes have not achieved glycemic control, and it is imperative that healthcare providers address the need for improved glycemic control[1].

Recommendations for Glycemic Goals

While the recommendations for glycemic goals are similar between the two clinical associations, the American Association of Clinical Endocrinologists (AACE) recommends a lower A1C target goal than the American Diabetes Association (ADA): ≤6.5% vs. <7.0%, respectively[5,6]. ADA and AACE also differ in recommendations for measuring blood glucose before and after eating. AACE uses fasting plasma glucose (FPG), defined as no caloric intake for at least 8 hours, while ADA uses preprandial capillary plasma glucose, which is similar but less stringent in terms of time interval. Likewise, the AACE uses postprandial glucose (PPG), defined as blood glucose levels 1 to 2 hours after the start of a meal, while the ADA refers to PPG as peak postprandial capillary plasma glucose (Table 1).

Warnings and Precautions for ONGLYZA

- **Use With Medications Known to Cause Hypoglycemia:** Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug

Treatment with ONGLYZA (saxagliptin), a dipeptidyl peptidase-4 (DPP4) inhibitor, along with diet and exercise, is an option in appropriate adult patients with type 2 diabetes. It offers improvements across key measures of glucose control. The safety and efficacy profiles of ONGLYZA were established through a rigorous clinical development program that included approximately 5,000 individuals (4,000 of whom received ONGLYZA), and it addresses unmet needs in type 2 diabetes by improving glycemic control for adults with type 2 diabetes. In clinical trials, ONGLYZA 2.5 mg and 5 mg were demonstrated to be effective at 24 weeks[7-10]. This Product Profiler reviews the evidence-based literature supporting ONGLYZA as a treatment for adults with type 2 diabetes to improve glycemic control as an adjunct to diet and exercise.

Disease State Overview

Diabetes is a group of metabolic diseases characterized by hyperglycemia, which is caused by insulin deficiency, insulin resistance, or both[11]. The most common form of diabetes is type 2, formerly called non-insulin dependent diabetes or adult-onset diabetes, which accounts for about 90% to 95% of all diagnosed cases[1].

Development of type 2 diabetes seems to be multifactorial, with genetic predisposition playing a large role. Other risk factors include obesity, increasing age, history of gestational diabetes, impaired glucose metabolism, and physical inactivity[5]. Race/ethnicity also contribute to the

TABLE 1
ADA and AACE Recommendations for Adults With Diabetes

ADA		AACE	
A1C	<7.0%	A1C	≤6.5%
Preprandial Capillary Plasma Glucose	70-130 mg/dL	FPG	<110 mg/dL
Peak Postprandial Capillary Plasma Glucose	<180 mg/dL	PPG	<140 mg/dL

FPG=fasting plasma glucose, PPG=postprandial glucose.
Sources: AACE 2007[5], ADA 2009[6]

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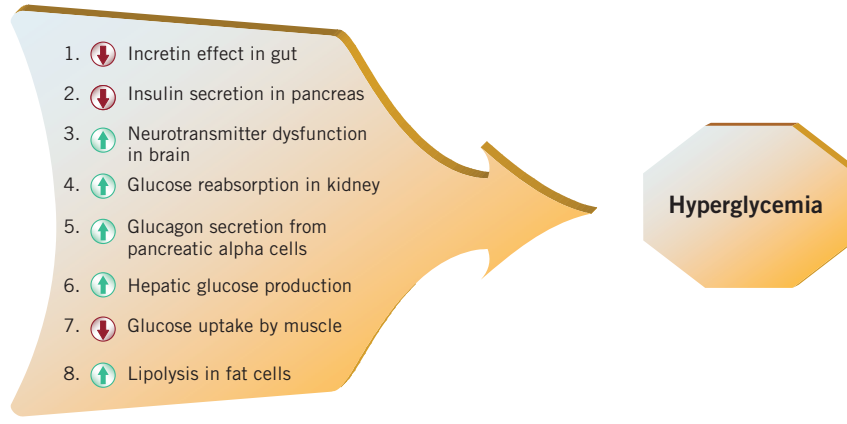
risk, and those at particularly high risk for developing type 2 diabetes include African Americans, Hispanic/Latino Americans, American Indians, Asian Americans, and Native Hawaiians or other Pacific Islanders[1].

Type 2 diabetes is a progressive disorder that usually begins as insulin resistance rather than a lack of insulin. The cells in muscle, liver, and fat do not use insulin properly, and as the need for insulin increases, the pancreas gradually loses its ability to produce it[12]. The conventional view of the progression of type 2 diabetes focuses primarily on insulin resistance and progressive beta cell failure resulting in insulin deficiency. Insulin acts to reduce blood glucose by signaling peripheral tissues to increase glucose uptake, promoting glycogen formation from glucose in the liver, and inhibiting secretion of glucagon from pancreatic alpha cells[13]. Glucagon acts as a counterbalancing force by enhancing hepatic glucose production and, under normal physiologic conditions, sustaining fasting plasma glucose[13]. Diabetes results from defective mechanisms of blood glucose regulation across several organ sites (Figure 1).

FIGURE 1
Organ Site Defects Involved in the Pathophysiology of Diabetes

The contributions of the ominous octet to hyperglycemia



Source: Adapted from DeFronzo 2008[14]

Once diagnosed, treatment for type 2 diabetes involves controlling glycemic parameters such as A1C, FPG, and PPG via lifestyle modifications such as diet and exercise, as well as pharmacological therapies. A1C measures the amount of serum glycated hemoglobin, a substance formed in red blood cells when glucose attaches to hemoglobin, and it provides a good estimate of how well the disease has been managed over the previous several months[6]. FPG measures glucose levels after a fasting period of 8 hours[6]. PPG measures blood glucose after a meal, which reflects an uptake of glucose in peripheral tissues.

Contribution of FPG and PPG to A1C

In patients with type 2 diabetes, insulin response is blunted and delayed, with higher and prolonged glucose excursions than those observed in people without type 2 diabetes[16]. Further, it has been demonstrated that FPG and PPG are abnormally elevated in patients with type 2 diabetes versus patients without diabetes[16]. Often, patients with uncontrolled type 2 diabetes experience increased daylong glycemia compared to those with controlled type 2 diabetes, because PPG levels are increased to a greater extent and do not return to premeal values. This results in an overall increase in plasma glucose concentrations[17].

Results from a study of 290 patients with type 2 diabetes who were divided into five quintiles of A1C levels revealed that the relative contribution of PPG to A1C level decreased as A1C level increased[18]. However, as A1C levels approached target glycemic levels (<7.3%), PPG was the major contributor to A1C level. Conversely, the contribution of FPG to A1C level increased gradually with diabetes worsening (≥9%) (Figure 2, page 4). Considering the contribution of FPG and PPG to A1C, the AACE recommends monitoring FPG and PPG as part of the patient's routine glycemic management[5].

The Role of Incretin Hormones

Intestinal peptides called incretins are involved in glucose homeostasis by signaling insulin secretion throughout the day and increasingly following a meal[19]. The two major incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide-1 (GLP-1), play a key role in type 2 diabetes and glucose control in

Most Common Adverse Reactions for ONGLYZA

Most common adverse reactions (regardless of investigator assessment of causality) reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%).

When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for ONGLYZA 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively.

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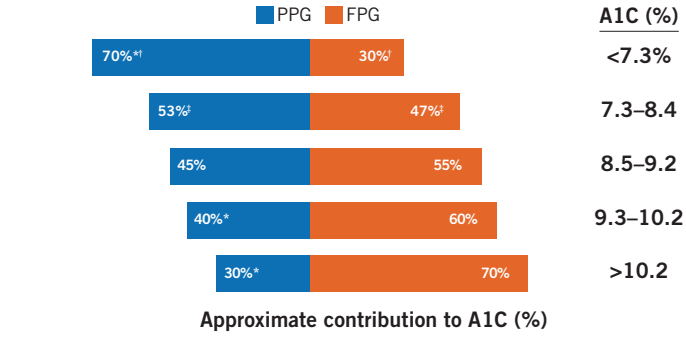
FIGURE 2
Contribution of PPG and FPG to A1C Levels

PPG and FPG differentially contribute to A1C levels depending on glycemic level



FPG=fasting plasma glucose, PPG=postprandial glucose.
*Significant difference was observed between fasting and postprandial plasma glucose.
†Significantly different from all other quintiles.
‡Significantly different from >10.2 quintile.
All percentages are approximate.

Source: Monnier 2003[18]

that they are increasingly released from the intestine in response to meals. Both hormones contribute to insulin secretion from the beginning of a meal, and their effects are amplified as plasma glucose concentrations rise. Specifically, these gut-produced hormones act on pancreatic islet cells (beta and alpha) to stimulate insulin and suppress glucagon secretion following caloric intake[19]. In healthy people, the effects of incretins account for up to 70% of glucose-induced insulin secretion, whereas, in those with type 2 diabetes, the effects of incretins are greatly diminished[19]. This diminished effect reduces insulin levels and increases glucagon levels after a meal, resulting in elevated PPG[19].

Understanding the role of incretins may provide insights into therapeutic strategies. It is important to note that incretins are rapidly degraded by the enzyme DPP4 within minutes[19]. Therapeutic approaches for enhancing incretin action include agents such as incretin mimetics, or degradation-resistant GLP-1 receptor agonists, as well as inhibitors of DPP4 enzyme activity[19].

Drug Interactions for ONGLYZA

Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, the dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Oral Antidiabetic Agents

Oral antidiabetic (OAD) agents are often grouped according to their glucose-lowering mechanisms of action, which target different aspects of diabetes pathophysiology. Insulin sensitizers reduce insulin resistance, whereas insulin secretagogues enhance the release of endogenous insulin. Other medications work by decreasing hepatic glucose output or by decreasing glucose absorption into the blood from the gastrointestinal tract. Diabetes is a complex disease with coexisting defects at multiple organ sites, and it is appropriate to treat patients using drug therapies of varying mechanisms of action in order to simultaneously target such defects[5]. Many of these agents may be used either as monotherapy or in combination for a synergistic effect, and a number of combination products have been designed to utilize these synergies[5]. The major classes of noninsulin anti-diabetic treatments include the following:

- Biguanides
- Thiazolidinediones (TZD)
- Sulfonylureas (SU)
- Meglitinides
- Alpha-glucosidase inhibitors (AGI)
- Synthetic amylin analogues
- Glucagon-like peptide-1 (GLP-1) receptor agonists
- Dipeptidyl-peptidase 4 (DPP4) inhibitors

DPP4 inhibitors and GLP-1 receptor agonists act on the incretin system and promote increased insulin release and decreased glucagon secretion from the pancreatic beta and alpha cells, respectively. The net effect is a decrease in blood glucose. ONGLYZA, a competitive DPP4 inhibitor, is a treatment that can be used in addition to diet and exercise to treat adult patients with type 2 diabetes to improve glycemic control. ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. ONGLYZA has not been studied in combination with insulin.

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Key Published Clinical Trials

The safety and efficacy of ONGLYZA were evaluated in six clinical trials, four of which have been published[7-10]. All efficacy analyses were performed using Analysis of Covariance (ANCOVA) and last-observation-carried-forward methodology on the primary endpoint of change from baseline to week 24 in A1C percentage.

Treatment with ONGLYZA at 2.5 mg or 5 mg doses produced clinically relevant and statistically significant reductions in all three key measures of glucose control studied — A1C, FPG, and PPG — when partnered with other commonly used oral anti-diabetic agents (metformin, the sulfonylurea glyburide, or a TZD), or when used as a monotherapy. ONGLYZA was weight and lipid neutral compared to placebo.

- ONGLYZA provided complementary A1C reductions when partnered with key OADs.
- ONGLYZA provided statistically significant A1C reduction when added to metformin.
- ONGLYZA added to metformin delivered statistically significant reductions in FPG and PPG.
- ONGLYZA added to the sulfonylurea glyburide provided improved glycemic control compared with double dose of glyburide.
- Overall incidence of adverse events was similar to placebo (72% vs. 71%, repectively). Discontinuation of therapy due to adverse events occurred in 3.3% and 1.8% of patients receiving ONGLYZA and placebo, respectively.

Warnings and Precautions for ONGLYZA

- **Use With Medications Known to Cause Hypoglycemia:** Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug

Most Common Adverse Reactions for ONGLYZA

Most common adverse reactions (regardless of investigator assessment of causality) reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%).

When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for ONGLYZA 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively.

Efficacy and Safety of ONGLYZA When Added to Metformin Therapy in Patients With Inadequately Controlled Type 2 Diabetes on Metformin Alone

In a randomized, double-blind, placebo-controlled trial, the safety and efficacy of ONGLYZA as add-on therapy was studied in adult patients with type 2 diabetes[7]. The trial included patients with uncontrolled type 2 diabetes, defined by A1C ≥7% and ≤10%. Patients had to be on metformin monotherapy for ≥8 weeks prior to screening. Patients were randomized to receive ONGLYZA 2.5 mg or 5 mg once daily, or placebo plus a stable dose of metformin (1,500–2,500 mg/day) for 24 weeks.

ONGLYZA add-on therapy demonstrated statistically significant reductions in A1C at Week 24 compared with metformin plus placebo (Figure 3, page 6). Placebo-corrected adjusted mean change in A1C from baseline was –0.7 and –0.8 for ONGLYZA 2.5 and 5 mg, respectively ($P<0.0001$). More patients treated with ONGLYZA achieved A1C <7% compared with patients receiving metformin plus placebo (37.1% and 43.5% for ONGLYZA 2.5 mg and 5 mg, respectively versus 16.6% for metformin plus placebo, $P\leq0.0001$).

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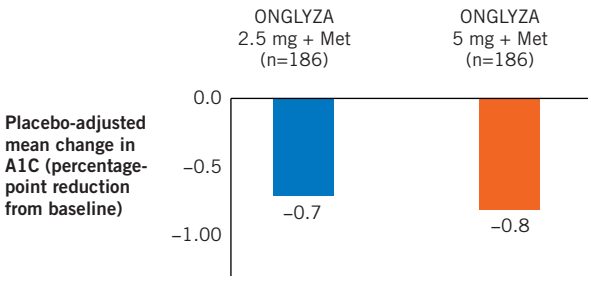
FIGURE 3
A1C Adjusted Mean Change From Baseline at 24 Weeks

Dose	ONGLYZA 2.5 mg + Met	ONGLYZA 5 mg + Met
n=	192	191
Baseline mean (%)	8.1	8.1



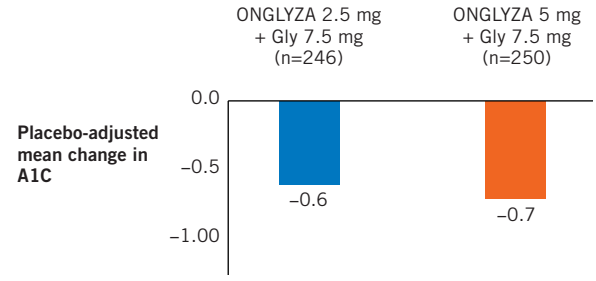
P≤0.0001 for both ONGLYZA groups vs. placebo

Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. Metformin dose was between 1500-2500 mg daily.

Met=metformin.
Source: ONGLYZA Prescribing Information[22]

FIGURE 4
A1C Adjusted Mean Change From Baseline at 24 Weeks

Dose	ONGLYZA 2.5 mg + Gly 7.5 mg	ONGLYZA 5 mg + Gly 7.5 mg
n=	248	253
Baseline mean (%)	8.4	8.5



P<0.0001 for both ONGLYZA groups vs. placebo plus uptitrated Gly

Intent-to-treat population using last observation on study prior to metformin rescue therapy.

Gly=glyburide.
Source: ONGLYZA Prescribing Information[22]

Safety Considerations

Incidence of hypoglycemia was 5.8% with ONGLYZA 5 mg plus metformin, 7.8% with ONGLYZA 2.5 mg plus metformin, and 5.0% with placebo plus metformin. Confirmed hypoglycemia (symptoms, with fingerstick glucose ≤50 mg/dL) was observed in 0.5% of patients treated with ONGLYZA and 0.6% of patients treated with metformin plus placebo.

From the trial data, the investigators concluded that in patients inadequately controlled on metformin alone, ONGLYZA add-on therapy improved glycemic indices. The addition of once-daily ONGLYZA to a stable dose of metformin was effective in reducing A1C in adult patients with type 2 diabetes.

ONGLYZA Added to a Submaximal Dose of Sulphonylurea Improves Glycaemic Control Compared With Uptitration of Sulphonylurea in Patients With Type 2 Diabetes: A Randomised Controlled Trial

A randomized, multicenter, double-blind, phase 3, international trial evaluated the safety and efficacy of ONGLYZA added to a submaximal dose of glyburide in 768 adult patients with uncontrolled type 2 diabetes (A1C ≥ 7.5% and ≤ 10.0%) taking a submaximal dose of glyburide alone[8]. Trial subjects included patients on submaximal glyburide therapy with inadequate glycemic control. Patients were randomized to receive once-daily ONGLYZA 2.5 mg plus glyburide, once-daily ONGLYZA 5 mg plus glyburide, or placebo plus uptitrated glyburide for 24 weeks. Blinded uptitration of glyburide was allowed in the glyburide-only arm to a maximum total daily dose of 15 mg. At Week 24, approximately 92% of glyburide-only patients were uptitrated to a total glyburide dose of 15 mg/day.

ONGLYZA 2.5 mg and 5 mg plus glyburide demonstrated an adjusted mean difference in A1C of –0.6 and –0.7 from uptitrated glyburide, respectively (Figure 4). Furthermore, a greater proportion of patients treated with ONGLYZA achieved A1C <7.0% at 24 weeks compared with placebo (22.4% for ONGLYZA 2.5 mg, 22.8% for ONGLYZA 5 mg, 9.1% for placebo [*P*<0.0001]).

Warnings and Precautions for ONGLYZA

- **Use with Medications Known to Cause Hypoglycemia:** Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug

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Safety Considerations

Incidence of hypoglycemia was 14.6% with ONGLYZA 5 mg plus glyburide, 13.3% with ONGLYZA 2.5 mg plus glyburide, and 10.1% with placebo plus uptitrated glyburide. Confirmed hypoglycemia (symptoms with fingerstick glucose ≤50 mg/dL) was reported by six patients (2.4%) treated with ONGLYZA 2.5 mg and two patients (0.8%) treated with ONGLYZA 5 mg compared with 2 patients (0.7%) treated with placebo plus glyburide.

In conclusion, this clinical trial demonstrated that the addition of ONGLYZA to glyburide therapy was effective in improving glycemic control in adults with type 2 diabetes inadequately controlled on glyburide monotherapy of submaximal dosing.

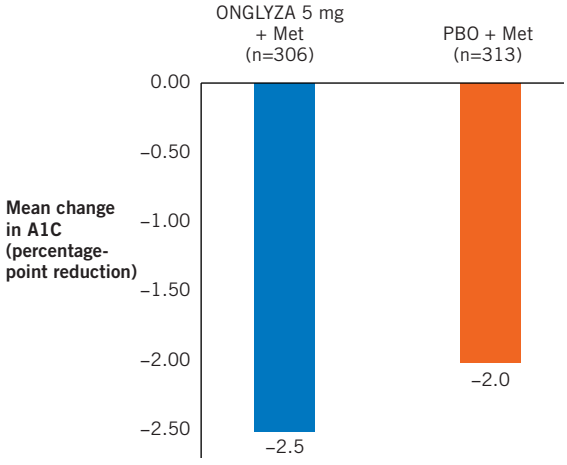
ONGLYZA Given in Combination With Metformin as Initial Therapy Improves Glycaemic Control in Patients With Type 2 Diabetes Compared With Either Monotherapy: a Randomized Controlled Trial

A multicenter, randomized, double-blind, active-controlled, phase 3 trial evaluated the efficacy and safety of initial combination therapy with ONGLYZA plus metformin compared to either as monotherapy[9]. The trial evaluated adult patients with type 2 diabetes and A1C ≥8 and ≤12% at screening. Patients were randomized to receive ONGLYZA 5 mg plus metformin or metformin plus placebo for 24 weeks. Metformin doses were titrated to a maximum dose of 2,000 mg/day in 500 mg/day increments over the first 5 weeks of the trial.

The primary efficacy endpoint was change in A1C from baseline to Week 24. At the end of the 24-week treatment period, ONGLYZA 5 mg plus metformin demonstrated a –0.5 adjusted mean difference in A1C from metformin (Figure 5). Additionally, the proportion of patients achieving A1C <7% was statistically significantly greater for ONGLYZA 5 mg plus metformin compared to metformin monotherapy (60.3% versus 41.1%, respectively [P<0.0001]).

FIGURE 5
A1C Mean Change From Baseline at 24 Weeks

Dose	ONGLYZA 5 mg + Met	PBO + Met
n=	306	313
Baseline mean (%)	9.4	9.4



P<0.0001 vs. metformin monotherapy

Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. Metformin was initiated at a starting dose of 500 mg daily, uptitrated to 1000 mg at Week one, and thereafter uptitrated as tolerated to a maximum of 2000 mg daily based on FPG through Week five.

Met=metformin, PBO=placebo.
Source: ONGLYZA Prescribing Information[22]

TABLE 2
Most Common Adverse Events (AEs)* (≥5%), Reported by Randomized Group

AEs, n (%)	ONGLYZA 5 mg + metformin (n=320)	Metformin (n=328)
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

*AEs do not include hypoglycemia events.
Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.
Source: ONGLYZA Prescribing Information[22]

Use in Specific Populations for ONGLYZA

Patients With Renal Impairment: The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CRCl] ≤50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

Pregnant and Nursing Women: There are no adequate and well-controlled studies in pregnant women. ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

Pediatric Patients: Safety and effectiveness of ONGLYZA in pediatric patients has not been established.

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Safety Considerations

The proportion of patients reporting adverse events was 55% for ONGLYZA 5 mg plus metformin vs. 59% for metformin plus placebo (Table 2). Incidence of hypoglycemia was 3.4% with ONGLYZA 5 mg with metformin vs. 4.0% with metformin plus placebo. There was one case of confirmed hypoglycemia (symptoms with fingerstick glucose ≤50 mg/dL) in the metformin monotherapy group. There were no cases of confirmed hypoglycemia in the ONGLYZA 5 mg plus metformin group.

Investigators concluded that combination therapy with ONGLYZA and metformin demonstrated a greater improvement in glycemic parameters compared with metformin alone. Combination therapy was effective as initial therapy to improve glycemic control in adults with type 2 diabetes.

Effect of ONGLYZA Monotherapy in Treatment-Naïve Patients With Type 2 Diabetes

The safety and efficacy of ONGLYZA were evaluated in a phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial[10]. Trial patients were treatment naïve with inadequately controlled type 2 diabetes (A1C ≥7% and ≤10% with diet and exercise at screening visit) and were between the ages of 18 and 77 years. In the trial, patients were randomized to receive ONGLYZA 2.5 mg, ONGLYZA 5 mg, or placebo once daily. The trial consisted of a 24-week treatment period in which patients were eligible to receive open-label metformin as a rescue therapy based on glycemic rescue criteria of FPG >240 mg/dL (13.3 mmol/L) at Weeks 4 and 6, FPG >220 mg/dL (12.2 mmol/L) at Week 8, or FPG >200 mg/dL (11.1 mmol/L) at Weeks 12, 16, 20, and 24.

ONGLYZA demonstrated a statistically significant reduction in the primary endpoint, change in A1C, from baseline to Week 24 compared with placebo ($P<0.0001$). Once-daily ONGLYZA 2.5 mg and 5 mg demonstrated a placebo-corrected adjusted mean change in A1C of –0.6 in both dosing groups (Figure 6).

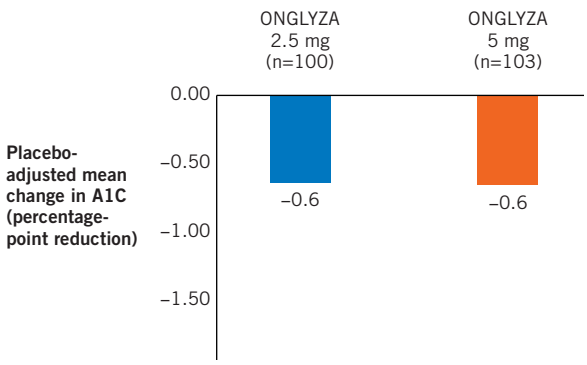
Safety Considerations

Incidence of hypoglycemia in two pooled monotherapy studies was 5.6% for ONGLYZA 5 mg, 4.0% for ONGLYZA 2.5 mg, and 4.1% for placebo. No cases of confirmed hypoglycemia (symptoms, with fingerstick glucose ≤50 mg/dL) were observed.

In conclusion, this clinical trial demonstrated that ONGLYZA monotherapy was effective in reducing A1C in adult treatment-naïve patients over a 24-week period while maintaining a tolerable safety profile.

FIGURE 6
A1C Adjusted Mean Change From Baseline at 24 Weeks

Dose	ONGLYZA 2.5 mg	ONGLYZA 5 mg
n=	102	106
Baseline mean (%)	7.9	8.0



P<0.0001 vs. placebo

Intent-to-treat population using last observation on study prior to metformin rescue therapy.

Source: ONGLYZA Prescribing Information[22]

Use in Specific Populations

Patients With Renal Impairment: The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CRCl] ≤50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

Pregnant and Nursing Women: There are no adequate and well-controlled studies in pregnant women. ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

Pediatric Patients: Safety and effectiveness of ONGLYZA in pediatric patients has not been established.

Please see US Full Prescribing Information on page 15.

ADVERSE REACTIONS[22]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The ONGLYZA full prescribing information lists all adverse reactions that occurred at a rate of 5% or higher. The following is a summary of significant adverse effects.

Monotherapy and Add-on Combination Therapy

In two placebo-controlled monotherapy trials of 24 weeks duration, patients were treated with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin. In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg was similar to placebo (72.0% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively (Table 3). The most common adverse events (reported in at least 2 patients treated with ONGLYZA 2.5 mg or at least 2 patients treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg, and more commonly than in patients treated with placebo are shown in Table 4.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo. In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%). In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide. The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of ONGLYZA on bone. An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

TABLE 3

Most Common Adverse Events (AEs)* Associated With Discontinuation of Therapy* (% of patients)

AEs	ONGLYZA 5 mg (n=882)	ONGLYZA 2.5 mg (n=882)	Placebo (n=799)
Lymphopenia	0.5%	0.1%	0.0%
Rash	0.3%	0.2%	0.3%
Blood creatinine increase	0.0%	0.3%	0.0%
Blood creatinine phosphokinase increase	0.2%	0.1%	0.0%

*Reported in at least 2 patients treated with ONGLYZA.
Source: ONGLYZA Prescribing Information[22]

TABLE 4

Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated With ONGLYZA 5 mg Plus Metformin and More Commonly Than in Patients Treated with Placebo

	Number (%) of Patients	
	ONGLYZA 5 mg n=882	Placebo n=799
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

*The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

Source: ONGLYZA Prescribing Information[22]

Please see US Full Prescribing Information on page 15.

TABLE 5
Initial Therapy With Combination of ONGLYZA and Metformin in Treatment-Naive Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly Than in Patients Treated With Metformin Alone)

	ONGLYZA 5 mg + Metformin* n=320	Metformin* n=328
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

*Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Source: ONGLYZA Prescribing Information[22]

Adverse Reactions Associated With ONGLYZA Coadministered With Metformin in Treatment-Naive Patients With Type 2 Diabetes

Table 5 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naive patients.

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6%) versus placebo (10.1%) (Table 6). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given ONGLYZA 5 mg plus metformin and 4.0% in patients given metformin alone.

TABLE 6
Incidence of Reported Hypoglycemia Across Phase 3 Clinical Trials
(% of patients)

	% of Patients		
	ONGLYZA 5 mg	ONGLYZA 2.5 mg	Comparator
Add-on to metformin	5.8	7.8	5.0
Initial combo to metformin	3.4	—	4.0
Add-on to glyburide	14.6	13.3	10.1
Add-on to a TZD	2.7	4.1	3.8
Pooled Monotherapy	5.6	4.0	4.1

TZD=thiazolidinedione.
Source: ONGLYZA Prescribing Information[22]

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Platelets

ONGLYZA did not demonstrate a clinically meaningful or consistent effect on platelet count in the six double-blind, controlled clinical safety and efficacy trials.

Please see US Full Prescribing Information on page 15.

P&T Committee Considerations

P&T decision makers must explore various aspects of a drug product when considering its place on a formulary. Points of interest often include efficacy, safety, availability of alternative agents, and cost. This section evaluates P&T considerations that apply to ONGLYZA.

Economic Impact of Type 2 Diabetes

While the health impact of diabetes is extensive, the economic impact is equally significant. It is estimated that 1 out of every 5 dollars spent on healthcare in the United States is spent caring for someone diagnosed with diabetes, and 1 in 10 healthcare dollars is attributed to the disease[23]. In 2007, the average annual healthcare cost for a person with diabetes was estimated to be $11,744, of which $6,649 (57%) was attributed to diabetes alone[23]. The estimated total healthcare costs totaled $174 billion. Of this expenditure, $116 billion was for direct medical expenses.

Type 2 diabetes was included in a study evaluating the cost and associated clinical outcomes of treating the 10 most prevalent diagnosed diseases in the aging male population (≥50 years of age)[24]. Data from a large national managed care database that included 30 health plans was analyzed in order to determine disease-specific economic outcomes and likelihood of experiencing a significant clinical event within 1 year of initiating treatment in the diseases of interest. Results showed that diabetes was ranked sixth out of the top 10 health conditions in 1-year, disease-specific medical costs. Investigators concluded that diabetes is a therapeutic area with great potential for improvement.

Due to the progressive nature of type 2 diabetes, many patients will, over time, require combination therapy to manage their glycemic control[25]. Over 40% of treated adults with type 2 diabetes have A1C levels higher than the ADA goal of <7%[3]. Evidence shows that failure to control hyperglycemia has a detrimental economic impact, and A1C control is pertinent not only from a clinical, but also from an economic standpoint[26]. Therefore, it is important to ensure access to drug therapy in order to help achieve and maintain glycemic goals for adult patients with type 2 diabetes.

ONGLYZA: A Treatment Option

Clinical trials have established that ONGLYZA, along with diet and exercise, is a treatment option in adults with type 2 diabetes, by helping improve glycemic control. When combined with metformin or glyburide, ONGLYZA improved glycemic control in adults with type 2 diabetes[7-9]. More than twice as many adults with type 2 diabetes treated with ONGLYZA 2.5 mg or 5 mg in addition to their current metformin or glyburide therapy achieved A1C <7% when compared with patients receiving placebo plus either metformin or uptitrated glyburide[7,8].

There is no dose adjustment required in patients with moderate to severe renal impairment or with end-stage renal disease (ESRD) requiring hemodialysis who are being treated with ONGLYZA 2.5 mg. A one-step dose adjustment to 2.5 mg is required for ONGLYZA 5 mg in patients with moderate to severe renal impairment or with end-stage renal disease (ESRD) requiring hemodialysis[22]. Assessment of renal function is recommended prior to the initiation of ONGLYZA and periodically thereafter. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. In addition, ONGLYZA 5 mg should be dose adjusted to 2.5 mg when coadministered with strong CYP3A4/5 inhibitors such as ketoconazole.

In pooled analysis from five clinical trials (two monotherapy trials and three add-on trials with metformin, thiazolidinedione, and glyburide), overall incidence of adverse events for ONGLYZA 2.5 mg and 5 mg was similar to placebo 72% vs. 71%, respectively[22]. Discontinuation of therapy due to adverse events occured in 3.3% and 1.8% of patients receiving ONGLYZA and placebo, respectively.

Type 2 diabetes takes an enormous toll, both physically and economically, and should be managed by early and clinically appropriate treatment. Both patients and managed care organizations can benefit from proactive management of type 2 diabetes[24].

Please see US Full Prescribing Information on page 15.

Indication, Safety and Tolerability, and Dosing

INDICATIONS AND USAGE[22]

Monotherapy and Combination Therapy

ONGLYZA (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

ONGLYZA has not been studied in combination with insulin.

CONTRAINDICATIONS[22]

None.

WARNINGS AND PRECAUTIONS[22]

Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

ADVERSE REACTIONS[22]

See pages 9-10.

DRUG INTERACTIONS[22]

Inducers of CYP3A4/5 Enzymes

Rifampin significantly decreased saxagliptin exposure with no change in the area under the time-concentration curve (AUC) of its active metabolite, 5-hydroxy saxagliptin. The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin. Therefore, dosage adjustment of ONGLYZA is not recommended.

Inhibitors of CYP3A4/5 Enzymes

Moderate Inhibitors of CYP3A4/5

Diltiazem increased the exposure of saxagliptin. Similar increases in plasma concentrations of saxagliptin are anticipated in the presence of other moderate CYP3A4/5 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil); however, dosage adjustment of ONGLYZA is not recommended.

Strong Inhibitors of CYP3A4/5

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor.

USE IN SPECIFIC POPULATIONS[22]

Pregnancy

Pregnancy Category B – There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed. Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1,503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7,986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1,432 and 992 times the MRHD. When administered to rats in combination with metformin, saxagliptin was not teratogenic nor embryolethal at exposures 21 times the saxagliptin MRHD. Combination administration of metformin with a higher dose of saxagliptin (109 times the saxagliptin MRHD) was associated with craniorachischisis (a rare neural tube defect characterized by incomplete closure of the skull and spinal column) in two fetuses from a single dam. Metformin exposures in each combination were 4 times the human exposure of 2000 mg daily. Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered ONGLYZA at any dose. Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

Please see US Full Prescribing Information on page 15.

Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function.

OVERDOSAGE[22]

In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

DOSAGE AND ADMINISTRATION[22]

Recommended Dosing

The recommended dose of ONGLYZA is 2.5 mg or 5 mg once daily taken regardless of meals.

Patients With Renal Impairment

No dosage adjustment for ONGLYZA is recommended for patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min). The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Because the dose of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. Renal function can be estimated from serum creatinine using the Cockcroft-Gault formula or Modification of Diet in Renal Disease formula.

Strong CYP3A4/5 Inhibitors

The dose of ONGLYZA is 2.5 mg once daily when co-administered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

HOW SUPPLIED/STORAGE AND HANDLING[22]

How Supplied

ONGLYZA (saxagliptin) tablets have markings on both sides and are available in 2.5 mg and 5 mg tablets.

Storage and Handling

Store at 20°–25°C (68°–77°F); excursions permitted to 15°–30°C (59°–86°F) [See USP Controlled Room Temperature].

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Conclusion

In view of the economic and overall health impact of type 2 diabetes, P&T decision makers understand the necessity of improving glycemic control in adults with type 2 diabetes. ONGLYZA provides an effective treatment option for adults with type 2 diabetes who have been inadequately controlled on diet and exercise with or without other OADs such as metformin, sulfonylurea, or a TZD. ONGLYZA is an appropriate option to consider for addition to a managed care drug formulary.

Treatment with ONGLYZA at 2.5 or 5 mg doses produced clinically relevant and statistically significant reductions in all three key measures of glucose control studied — A1C, FPG, and PPG — when partnered with other commonly used oral anti-diabetic agents (metformin, the sulfonylurea glyburide, or a TZD), or when used as a monotherapy. ONGLYZA was weight and lipid neutral compared to placebo.

- ONGLYZA provided complementary A1C reductions when partnered with key OADs.
- ONGLYZA provided statistically significant A1C reduction when added to metformin.
- ONGLYZA added to metformin delivered statistically significant reductions in FPG and PPG.
- ONGLYZA added to the sulfonylurea glyburide provided improved glycemic control compared to double dose of glyburide.
- Overall incidence of adverse events was similar to placebo (72% vs. 71%, repectively). Discontinuation of therapy due to adverse events occurred in 3.3% and 1.8% of patients receiving ONGLYZA and placebo, respectively.

Important Limitations of Use for ONGLYZA

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. ONGLYZA has not been studied in combination with insulin.

Warnings and Precautions for ONGLYZA

• Use with Medications Known to Cause Hypoglycemia: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA
• Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug

Most Common Adverse Reactions for ONGLYZA

Most common adverse reactions (regardless of investigator assessment of causality) reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%). When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for ONGLYZA 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively.

Please see US Full Prescribing Information on page 15.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONGLYZA safely and effectively. See full prescribing information for ONGLYZA.

ONGLYZA (saxagliptin) tablets

Initial U.S. Approval: 2009

INDICATIONS AND USAGE

ONGLYZA is a dipeptidyl peptidase-4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

Important limitations of use:

- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.2)
- Has not been studied in combination with insulin. (1.2)

DOSAGE AND ADMINISTRATION

- The recommended dose is 2.5 mg or 5 mg once daily taken regardless of meals. (2.1)
- 2.5 mg daily is recommended for patients with moderate or severe renal impairment, or end-stage renal disease (CrCl ≤50 mL/min). Assess renal function prior to initiation of ONGLYZA and periodically thereafter. (2.2)
- 2.5 mg daily is recommended for patients also taking strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole). (2.3, 7.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg and 2.5 mg (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- When used with an insulin secretagogue (e.g., sulfonylurea), a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia. (5.1)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA (saxagliptin) or any other antidiabetic drug. (5.2)

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with placebo are: upper respiratory tract infection, urinary tract infection, and headache. (6.1)
- Peripheral edema was reported more commonly in patients treated with the combination of ONGLYZA and a thiazolidinedione (TZD) than in patients treated with the combination of placebo and TZD. (6.1)
- Hypoglycemia was reported more commonly in patients treated with the combination of ONGLYZA and sulfonylurea than in patients treated with the combination of placebo and sulfonylurea. (6.1)
- Hypersensitivity-related events (e.g., urticaria, facial edema) were reported more commonly in patients treated with ONGLYZA than in patients treated with placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

- Coadministration with strong CYP3A4/5 inhibitors (e.g., ketoconazole) significantly increases saxagliptin concentrations. Recommend limiting ONGLYZA dose to 2.5 mg once daily. (2.3, 7.2)

USE IN SPECIFIC POPULATIONS

- There are no adequate and well-controlled studies in pregnant women. (8.1)
- Safety and effectiveness of ONGLYZA in pediatric patients below the age of 18 have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

ONGLYZA (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [See *Clinical Studies (14).*]

1.2 Important Limitations of Use

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

ONGLYZA has not been studied in combination with insulin.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of ONGLYZA is 2.5 mg or 5 mg once daily taken regardless of meals.

2.2 Patients with Renal Impairment

No dosage adjustment for ONGLYZA is recommended for patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min).

The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Because the dose of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. Renal function can be estimated from serum creatinine using the Cockcroft-Gault formula or Modification of Diet in Renal Disease formula. [See *Clinical Pharmacology (12.3).*]

2.3 Strong CYP3A4/5 Inhibitors

The dose of ONGLYZA is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). [See *Drug Interactions (7.2)* and *Clinical Pharmacology (12.3).*]

3 DOSAGE FORMS AND STRENGTHS

- ONGLYZA (saxagliptin) 5 mg tablets are pink, biconvex, round, film-coated tablets with "5" printed on one side and "4215" printed on the reverse side, in blue ink.
- ONGLYZA (saxagliptin) 2.5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with "2.5" printed on one side and "4214" printed on the reverse side, in blue ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA. [See *Adverse Reactions (6.1).*]

5.2 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Monotherapy and Add-On Combination Therapy

In two placebo-controlled monotherapy trials of 24-weeks duration, patients were treated with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg was similar to placebo (72.0% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse events (reported in at least 2 patients treated with ONGLYZA 2.5 mg or at least 2 patients treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	ONGLYZA 5 mg N=882	Placebo N=799
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

Adverse Reactions Associated with ONGLYZA Coadministered with Metformin in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naive patients.

Table 2: Initial Therapy with Combination of ONGLYZA and Metformin in Treatment-Naive Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly than in Patients Treated with Metformin Alone)

	Number (%) of Patients	
	ONGLYZA 5 mg + Metformin* N=320	Metformin* N=328
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6%) versus placebo (10.1%). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given ONGLYZA 5 mg plus metformin and 4.0% in patients given metformin alone.

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Platelets

ONGLYZA did not demonstrate a clinically meaningful or consistent effect on platelet count in the six, double-blind, controlled clinical safety and efficacy trials.

7 DRUG INTERACTIONS

7.1 Inducers of CYP3A4/5 Enzymes

Rifampin significantly decreased saxagliptin exposure with no change in the area under the time-concentration curve (AUC) of its active metabolite, 5-hydroxy saxagliptin. The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin. Therefore, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology (12.3)*.]

7.2 Inhibitors of CYP3A4/5 Enzymes

Moderate Inhibitors of CYP3A4/5

Diltiazem increased the exposure of saxagliptin. Similar increases in plasma concentrations of saxagliptin are anticipated in the presence of other moderate CYP3A4/5 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil); however, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology (12.3)*.]

Strong Inhibitors of CYP3A4/5

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*.]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD. When administered to rats in combination with metformin, saxagliptin was not teratogenic nor embryolethal at exposures 21 times the saxagliptin MRHD. Combination administration of metformin with a higher dose of saxagliptin (109 times the saxagliptin MRHD) was associated with craniorachischisis (a rare neural tube defect characterized by incomplete closure of the skull and spinal column) in two fetuses from a single dam. Metformin exposures in each combination were 4 times the human exposure of 2000 mg daily.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

8.3 Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*.]

10 OVERDOSAGE

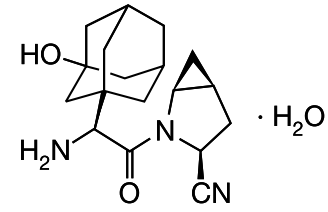
In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

11 DESCRIPTION

Saxagliptin is an orally-active inhibitor of the DPP4 enzyme.

Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2 \bullet H_2O$ and the molecular weight is 333.43. The structural formula is:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

12.2 Pharmacodynamics

In patients with type 2 diabetes mellitus, administration of ONGLYZA inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, ONGLYZA was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

ONGLYZA™ (saxagliptin)

12.3 Pharmacokinetics

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Absorption

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. ONGLYZA may be administered with or without food.

Distribution

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite. [See *Drug Interactions (7)*.]

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of ONGLYZA 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Specific Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment (N=8 per group) compared to subjects with normal renal function. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease on hemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \{\times 0.85 \text{ for female patients}\}}{[72 \times \text{serum creatinine (mg/dL)}]}$$

The degree of renal impairment did not affect the C_{max} of saxagliptin or its active metabolite. In subjects with mild renal impairment, the AUC values of saxagliptin and its active metabolite were 20% and 70% higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not considered to be clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment, the AUC values of saxagliptin and its active metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. To achieve plasma exposures of saxagliptin and its active metabolite similar to those in patients with normal renal function, the recommended dose is 2.5 mg once daily in patients with moderate and severe renal impairment, as well as in patients with end-stage renal disease requiring hemodialysis. Saxagliptin is removed by hemodialysis.

Hepatic Impairment

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful. No dosage adjustment is recommended for patients with hepatic impairment.

Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Geriatric

No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for saxagliptin than young subjects (18-40 years). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Pediatric

Studies characterizing the pharmacokinetics of saxagliptin in pediatric patients have not been performed.

Race and Ethnicity

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions

The metabolism of saxagliptin is primarily mediated by CYP3A4/5.

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate but is not a significant inhibitor or inducer of P-gp.

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Thus, protein binding would not have a meaningful influence on the pharmacokinetics of saxagliptin or other drugs.

In Vivo Assessment of Drug Interactions

Effects of Saxagliptin on Other Drugs

In studies conducted in healthy subjects, as described below, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-2 substrate, did not alter the pharmacokinetics of metformin in healthy subjects. Therefore, ONGLYZA is not an inhibitor of hOCT-2-mediated transport.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the plasma C_{max} of glyburide by 16%; however, the AUC of glyburide was unchanged. Therefore, ONGLYZA does not meaningfully inhibit CYP2C9-mediated metabolism.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 substrate, increased the plasma C_{max} of pioglitazone by 14%; however, the AUC of pioglitazone was unchanged.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of digoxin. Therefore, ONGLYZA is not an inhibitor or inducer of P-gp-mediated transport.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, did not alter the pharmacokinetics of simvastatin. Therefore, ONGLYZA is not an inhibitor or inducer of CYP3A4/5-mediated metabolism.

Diltiazem: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the plasma C_{max} of diltiazem by 16%; however, the AUC of diltiazem was unchanged.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and multiple doses of ketoconazole (200 mg every 12 hours at steady state), a strong inhibitor of CYP3A4/5 and P-gp, decreased the plasma C_{max} and AUC of ketoconazole by 16% and 13%, respectively.

Effects of Other Drugs on Saxagliptin

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the C_{max} of saxagliptin by 8%; however, the AUC of saxagliptin was unchanged.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of saxagliptin.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged.

Diltiazem: Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} of saxagliptin by 63% and the AUC by 2.1-fold. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 44% and 36%, respectively.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a strong inhibitor of CYP3A4/5 and P-gp, increased the C_{max} for saxagliptin by 62% and the AUC by 2.5-fold. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 95% and 91%, respectively.

In another study, coadministration of a single dose of saxagliptin (20 mg) and ketoconazole (200 mg every 12 hours at steady state), increased the C_{max} and AUC of saxagliptin by 2.4-fold and 3.7-fold, respectively. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 96% and 90%, respectively.

Rifampin: Coadministration of a single dose of saxagliptin (5 mg) and rifampin (600 mg QD at steady state) decreased the C_{max} and AUC of saxagliptin by 53% and 76%, respectively, with a corresponding increase in C_{max} (39%) but no significant change in the plasma AUC of the active metabolite.

Omeprazole: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin.

Aluminum hydroxide + magnesium hydroxide + simethicone: Coadministration of a single dose of saxagliptin (10 mg) and a liquid containing aluminum hydroxide (2400 mg), magnesium hydroxide (2400 mg), and simethicone (240 mg) decreased the C_{max} of saxagliptin by 26%; however, the AUC of saxagliptin was unchanged.

Famotidine: Administration of a single dose of saxagliptin (10 mg) 3 hours after a single dose of famotidine (40 mg), an inhibitor of hOCT-1, hOCT-2, and hOCT-3, increased the C_{max} of saxagliptin by 14%; however, the AUC of saxagliptin was unchanged.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Saxagliptin did not induce tumors in either mice (50, 250, and 600 mg/kg) or rats (25, 75, 150, and 300 mg/kg) at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 870 (males) and 1165 (females) times the human exposure at the MRHD of 5 mg/day. In rats, exposures were approximately 355 (males) and 2217 (females) times the MRHD.

Saxagliptin was not mutagenic or clastogenic with or without metabolic activation in an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo*/*in vitro* cytogenetics study in rat peripheral blood lymphocytes. The active metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

In a rat fertility study, males were treated with oral gavage doses for 2 weeks prior to mating, during mating, and up to scheduled termination (approximately 4 weeks total) and females were treated with oral gavage doses for 2 weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at exposures of approximately 603 (males) and 776 (females) times the MRHD. Higher doses that elicited maternal toxicity also increased fetal resorptions (approximately 2069 and 6138 times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138 times the MRHD.

13.2 Animal Toxicology

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible at ≥20 times the MRHD but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1 to 3 times) the MRHD of 5 mg. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

14 CLINICAL STUDIES

ONGLYZA has been studied as monotherapy and in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone) therapy. ONGLYZA has not been studied in combination with insulin.

A total of 4148 patients with type 2 diabetes mellitus were randomized in six, double-blind, controlled clinical trials conducted to evaluate the safety and glycemic efficacy of ONGLYZA. A total of 3021 patients in these trials were treated with ONGLYZA. In these trials, the mean age was 54 years, and 71% of patients were Caucasian, 16% were Asian, 4% were black, and 9% were of other racial groups. An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of 6 to 12 weeks in duration.

In these six, double-blind trials, ONGLYZA was evaluated at doses of 2.5 mg and 5 mg once daily. Three of these trials also evaluated a saxagliptin dose of 10 mg daily. The 10 mg daily dose of saxagliptin did not provide greater efficacy than the 5 mg daily dose. Treatment with ONGLYZA at all doses produced clinically relevant and statistically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

ONGLYZA was not associated with significant changes from baseline in body weight or fasting serum lipids compared to placebo.

14.1 Monotherapy

A total of 766 patients with type 2 diabetes inadequately controlled on diet and exercise (A1C ≥7% to ≤10%) participated in two 24-week, double-blind, placebo-controlled trials evaluating the efficacy and safety of ONGLYZA monotherapy.

In the first trial, following a 2-week single-blind diet, exercise, and placebo lead-in period, 401 patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy, added on to placebo or ONGLYZA. Efficacy was evaluated at the last measurement prior to rescue therapy for patients needing rescue. Dose titration of ONGLYZA was not permitted.

Treatment with ONGLYZA 2.5 mg and 5 mg daily provided significant improvements in A1C, FPG, and PPG compared to placebo (Table 3). The percentage of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 16% in the ONGLYZA 2.5 mg treatment group, 20% in the ONGLYZA 5 mg treatment group, and 26% in the placebo group.

Table 3: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA Monotherapy in Patients with Type 2 Diabetes*

Efficacy Parameter	ONGLYZA 2.5 mg N=102	ONGLYZA 5 mg N=106	Placebo N=95
Hemoglobin A1C (%)	**N=100**	**N=103**	**N=92**
Baseline (mean)	7.9	8.0	7.9
Change from baseline (adjusted mean†)	−0.4	−0.5	+0.2
Difference from placebo (adjusted mean†)	−0.6‡	−0.6‡	
95% Confidence Interval	(−0.9, −0.3)	(−0.9, −0.4)	
Percent of patients achieving A1C <7%	35% (35/100)	38%§ (39/103)	24% (22/92)
Fasting Plasma Glucose (mg/dL)	**N=101**	**N=105**	**N=92**
Baseline (mean)	178	171	172
Change from baseline (adjusted mean†)	−15	−9	+6
Difference from placebo (adjusted mean†)	−21§	−15§	
95% Confidence Interval	(−31, −10)	(−25, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=78**	**N=84**	**N=71**
Baseline (mean)	279	278	283
Change from baseline (adjusted mean†)	−45	−43	−6
Difference from placebo (adjusted mean†)	−39¶	−37§	
95% Confidence Interval	(−61, −16)	(−59, −15)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo
§ p-value <0.05 compared to placebo
¶ Significance was not tested for the 2-hour PPG for the 2.5 mg dose of ONGLYZA.

A second 24-week monotherapy trial was conducted to assess a range of dosing regimens for ONGLYZA. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of ONGLYZA, or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or ONGLYZA; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either ONGLYZA 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of −0.4% and −0.3%, respectively). Treatment with ONGLYZA 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of −0.4%).

14.2 Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1500-2550 mg daily) for at least 8 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily, for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin.

Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of ONGLYZA and metformin were not permitted.

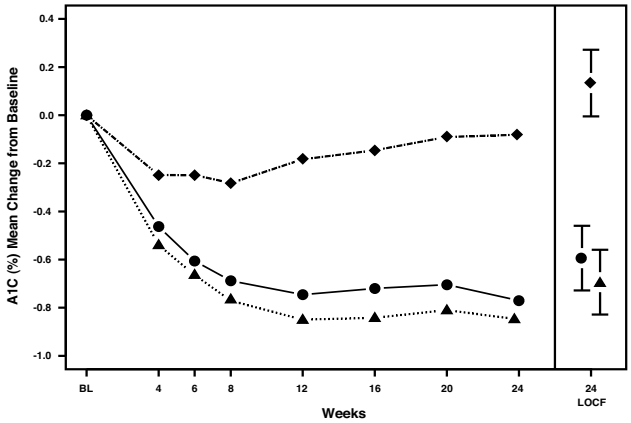
ONGLYZA 2.5 mg and 5 mg add-on to metformin provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin (Table 4). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the ONGLYZA 2.5 mg add-on to metformin group, 13% in the ONGLYZA 5 mg add-on to metformin group, and 27% in the placebo add-on to metformin group.

Table 4: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Metformin*

Efficacy Parameter	ONGLYZA 2.5 mg + Metformin N=192	ONGLYZA 5 mg + Metformin N=191	Placebo + Metformin N=179
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

Figure 1: Mean Change from Baseline in A1C in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin*



* Includes patients with a baseline and week 24 value. Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

Add-On Combination Therapy with a Thiazolidinedione

A total of 565 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a thiazolidinedione (TZD) in patients with inadequate glycemic control (A1C ≥7% to ≤10.5%) on TZD alone. To qualify for enrollment, patients were required to be on a stable dose of pioglitazone (30-45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medications. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator's discretion if believed to be medically appropriate.

ONGLYZA 2.5 mg and 5 mg add-on to TZD provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to TZD (Table 5). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 10% in the ONGLYZA 2.5 mg add-on to TZD group, 6% for the ONGLYZA 5 mg add-on to TZD group, and 10% in the placebo add-on to TZD group.

Table 5: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with a Thiazolidinedione*

Efficacy Parameter	ONGLYZA 2.5 mg + TZD N=195	ONGLYZA 5 mg + TZD N=186	Placebo + TZD N=184
Hemoglobin A1C (%)	**N=192**	**N=183**	**N=180**
Baseline (mean)	8.3	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.9	−0.3
Difference from placebo (adjusted mean†)	−0.4§	−0.6‡	
95% Confidence Interval	(−0.6, −0.2)	(−0.8, −0.4)	
Percent of patients achieving A1C <7%	42%§ (81/192)	42%§ (77/184)	26% (46/180)
Fasting Plasma Glucose (mg/dL)	**N=193**	**N=185**	**N=181**
Baseline (mean)	163	160	162
Change from baseline (adjusted mean†)	−14	−17	−3
Difference from placebo (adjusted mean†)	−12§	−15§	
95% Confidence Interval	(−20, −3)	(−23, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=156**	**N=134**	**N=127**
Baseline (mean)	296	303	291
Change from baseline (adjusted mean†)	−55	−65	−15
Difference from placebo (adjusted mean†)	−40§	−50§	
95% Confidence Interval	(−56, −24)	(−66, −34)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + TZD
§ p-value <0.05 compared to placebo + TZD

Add-On Combination Therapy with Glyburide

A total of 768 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a sulfonylurea (SU) in patients with inadequate glycemic control at enrollment (A1C ≥7.5% to ≤10%) on a submaximal dose of SU alone. To qualify for enrollment, patients were required to be on a submaximal dose of SU for 2 months or greater. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period, and placed on glyburide 7.5 mg once daily. Following the lead-in period, eligible patients with A1C ≥7% to ≤10% were randomized to either 2.5 mg or 5 mg of ONGLYZA add-on to 7.5 mg glyburide or to placebo plus a 10 mg total daily dose of glyburide. Patients who received placebo were eligible to have glyburide up-titrated to a total daily dose of 15 mg. Up-titration of glyburide was not permitted in patients who received ONGLYZA 2.5 mg or 5 mg. Glyburide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glyburide group were up-titrated to a final total daily dose of 15 mg during the first 4 weeks of the study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medication. Dose titration of ONGLYZA was not permitted during the study.

In combination with glyburide, ONGLYZA 2.5 mg and 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus up-titrated glyburide group (Table 6). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 18% in the ONGLYZA 2.5 mg add-on to glyburide group, 17% in the ONGLYZA 5 mg add-on to glyburide group, and 30% in the placebo plus up-titrated glyburide group.

Table 6: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Glyburide*

Efficacy Parameter	ONGLYZA 2.5 mg + Glyburide 7.5 mg N=248	ONGLYZA 5 mg + Glyburide 7.5 mg N=253	Placebo + Up-Titrated Glyburide N=267
Hemoglobin A1C (%)	**N=246**	**N=250**	**N=264**
Baseline (mean)	8.4	8.5	8.4
Change from baseline (adjusted mean†)	–0.5	–0.6	+0.1
Difference from up-titrated glyburide (adjusted mean†)	–0.6‡	–0.7‡	
95% Confidence Interval	(–0.8, –0.5)	(–0.9, –0.6)	
Percent of patients achieving A1C <7%	22%§ (55/246)	23%§ (57/250)	9% (24/264)
Fasting Plasma Glucose (mg/dL)	**N=247**	**N=252**	**N=265**
Baseline (mean)	170	175	174
Change from baseline (adjusted mean†)	–7	–10	+1
Difference from up-titrated glyburide (adjusted mean†)	–8§	–10§	
95% Confidence Interval	(–14, –1)	(–17, –4)	
2-hour Postprandial Glucose (mg/dL)	**N=195**	**N=202**	**N=206**
Baseline (mean)	309	315	323
Change from baseline (adjusted mean†)	–31	–34	+8
Difference from up-titrated glyburide (adjusted mean†)	–38§	–42§	
95% Confidence Interval	(–50, –27)	(–53, –31)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + up-titrated glyburide
§ p-value <0.05 compared to placebo + up-titrated glyburide

Coadministration with Metformin in Treatment-Naive Patients

A total of 1306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA coadministered with metformin in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: ONGLYZA 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. ONGLYZA was dosed once daily. In the 3 treatment groups using metformin, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Coadministration of ONGLYZA 5 mg plus metformin provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin (Table 7).

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=320	Placebo + Metformin N=328
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	–2.5	–2.0
Difference from placebo + metformin (adjusted mean†)	–0.5‡	
95% Confidence Interval	(–0.7, –0.4)	
Percent of patients achieving A1C <7%	60%§ (185/307)	41% (129/314)

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

(Continued)

Table 7: (Continued) Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=320	Placebo + Metformin N=328
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean†)	–60	–47
Difference from placebo + metformin (adjusted mean†)	–13§	
95% Confidence Interval	(–19, –6)	
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean†)	–138	–97
Difference from placebo + metformin (adjusted mean†)	–41§	
95% Confidence Interval	(–57, –25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.
† Least squares mean adjusted for baseline value.
‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONGLYZA™ (saxagliptin) tablets have markings on both sides and are available in the strengths and packages listed in Table 8.

Table 8: ONGLYZA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
5 mg	pink biconvex, round	"5" on one side and "4215" on the reverse, in blue ink	Bottles of 30	0003-4215-11
			Bottles of 90	0003-4215-21
			Bottles of 500	0003-4215-31
			Blister of 100	0003-4215-41
2.5 mg	pale yellow to light yellow biconvex, round	"2.5" on one side and "4214" on the reverse, in blue ink	Bottles of 30	0003-4214-11
			Bottles of 90	0003-4214-21

Storage and Handling

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

17.1 Instructions

Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Physicians should instruct their patients to read the Patient Package Insert before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom or if any existing symptom persists or worsens.

17.2 Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

Manufactured by:
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Princeton, NJ 08543 USA
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