

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, for oral use

Initial U.S. Approval: 2009

INDICATIONS AND USAGE

ONGLYZA is a dipeptidyl peptidase-4 (DPP4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings. (1.1, 14)

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 patients with a history of pancreatitis (1.2, 5.1)

DOSAGE AND ADMINISTRATION

- Recommended dosage is 2.5 mg or 5 mg once daily taken regardless of meals. (2.1)
- Patients with moderate or severe renal impairment, or end-stage renal disease (CrCl \leq 50 mL/min): Recommended dosage is 2.5 mg once daily regardless of meals. (2.2)
- Assess renal function before starting 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, 7.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg and 2.5 mg (3)

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to ONGLYZA. (4)

WARNINGS AND PRECAUTIONS

- *Acute Pancreatitis (postmarketing reports)*: If pancreatitis is suspected, promptly discontinue ONGLYZA. (5.1)
- *Hypoglycemia*: In add-on to sulfonylurea, add-on to insulin, and add-on to metformin plus sulfonylurea trials, confirmed hypoglycemia was more common in patients treated with ONGLYZA compared to placebo.

When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.2, 6.1)

- *Hypersensitivity-Related Events (e.g., urticaria, facial edema)*: More common in patients treated with ONGLYZA than in patients treated with placebo; and postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions. Promptly discontinue ONGLYZA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.3, 6.1, 6.2)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug. (5.4)

ADVERSE REACTIONS

- Adverse reactions reported in \geq 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)

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

- *Strong CYP3A4/5 inhibitors (e.g., ketoconazole)*: Coadministration with ONGLYZA significantly increases saxagliptin concentrations. Recommend limiting ONGLYZA dosage to 2.5 mg once daily. (2.3, 7.1)

USE IN SPECIFIC POPULATIONS

- No adequate and well-controlled studies in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Monotherapy and Combination Therapy
- 1.2 Important Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Dosage in Patients with Renal Impairment
- 2.3 Dosage Adjustment with Concomitant Use of Strong CYP3A4/5 Inhibitors
- 2.4 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Pancreatitis
- 5.2 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin
- 5.3 Hypersensitivity Reactions
- 5.4 Macrovascular Outcomes

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Strong Inhibitors of CYP3A4/5 Enzymes

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Monotherapy
- 14.2 Combination Therapy
- 14.3 Renal Impairment

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*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 is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings. [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 patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using ONGLYZA. [See *Warnings and Precautions (5.1)*.]

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ONGLYZA is 2.5 mg or 5 mg once daily taken regardless of meals. ONGLYZA tablets must not be split or cut.

2.2 Dosage in Patients with Renal Impairment

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

The dosage of ONGLYZA is 2.5 mg once daily (regardless of meals) for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min) [see *Clinical Pharmacology (12.3)* and *Clinical Studies (14.3)*]. ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Because the dosage 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 Dosage Adjustment with Concomitant Use of Strong CYP3A4/5 Inhibitors

The dosage 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* (7.1) and *Clinical Pharmacology* (12.3).]

2.4 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When ONGLYZA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. [See *Warnings and Precautions* (5.2).]

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

ONGLYZA is contraindicated in patients with a history of a serious hypersensitivity reaction to ONGLYZA, such as anaphylaxis, angioedema, or exfoliative skin conditions. [See *Warnings and Precautions* (5.3) and *Adverse Reactions* (6.2).]

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis in patients taking ONGLYZA. After initiation of ONGLYZA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, ONGLYZA should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ONGLYZA.

5.2 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

When ONGLYZA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. [See *Adverse Reactions (6.1)*.] Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with ONGLYZA. [See *Dosage and Administration (2.4)*.]

5.3 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with ONGLYZA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with ONGLYZA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue ONGLYZA, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions (6.2)*.]

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with ONGLYZA.

5.4 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.

Adverse Reactions with Monotherapy and with 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. The 10 mg dosage is not an approved dosage.

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% 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 $\geq 5\%$ 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 in Placebo-Controlled Trials* Reported in $\geq 5\%$ 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 $\geq 5\%$ and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in $\geq 2\%$ of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and $\geq 1\%$ 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 10 mg dosage is not an approved dosage. 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.

Adverse Reactions in Patients with Renal Impairment

ONGLYZA 2.5 mg was compared to placebo in a 12-week trial in 170 patients with type 2 diabetes and moderate or severe renal impairment or end-stage renal disease (ESRD). The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo.

Adverse Reactions with Concomitant Use with Insulin

In the add-on to insulin trial [see *Clinical Studies (14.2)*], the incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo, except for confirmed hypoglycemia [see *Adverse Reactions (6.1)*].

Adverse Reactions with Concomitant Use with Metformin in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in $\geq 5\%$ 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 in $\geq 5\%$ 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 or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

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 [see *Warnings and Precautions (5.2)*]. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4% 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-naïve patients given ONGLYZA 5 mg plus metformin and 4% in patients given metformin alone.

In the active-controlled trial comparing add-on therapy with ONGLYZA 5 mg to glipizide in patients inadequately controlled on metformin alone, the incidence of reported hypoglycemia was 3% (19 events in 13 patients) with ONGLYZA 5 mg versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤ 50 mg/dL) was reported in none of the ONGLYZA-treated patients and in 35 glipizide-treated patients (8.1%) ($p < 0.0001$).

During 12 weeks of treatment in patients with moderate or severe renal impairment or ESRD, the overall incidence of reported hypoglycemia was 20% among patients treated with ONGLYZA 2.5 mg and 22% among patients treated with placebo. Four ONGLYZA-treated patients (4.7%) and three placebo-treated patients (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤ 50 mg/dL).

In the add-on to insulin trial, the overall incidence of reported hypoglycemia was 18.4% for ONGLYZA 5 mg and 19.9% for placebo. However, the incidence of confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤ 50 mg/dL) was higher with ONGLYZA 5 mg (5.3%) versus placebo (3.3%).

In the add-on to metformin plus sulfonylurea trial, the overall incidence of reported hypoglycemia was 10.1% for ONGLYZA 5 mg and 6.3% for placebo. Confirmed hypoglycemia

was reported in 1.6% of the ONGLYZA-treated patients and in none of the placebo-treated patients [see *Warnings and Precautions (5.2)*].

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 ONGLYZA-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Infections

In the unblinded, controlled, clinical trial database for ONGLYZA to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 ONGLYZA-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with ONGLYZA until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of ONGLYZA that remained stable throughout ONGLYZA treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with ONGLYZA use. Causality has not been estimated and there are too few cases to date to determine whether tuberculosis is related to ONGLYZA use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in an ONGLYZA-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of ONGLYZA therapy. There have been no spontaneous reports of opportunistic infections associated with ONGLYZA use.

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 ONGLYZA 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 10 mg dosage is not an approved dosage.

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.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of ONGLYZA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions. [See *Contraindications (4)* and *Warnings and Precautions (5.3)*.]

Mutagenesis

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.

Impairment of Fertility

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 and/or Pharmacology

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.

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. The 10 mg dosage is not an approved dosage. Treatment with ONGLYZA 5 mg and 2.5 mg 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.

ONGLYZA has also been evaluated in four additional trials in patients with type 2 diabetes: an active-controlled trial comparing add-on therapy with ONGLYZA to glipizide in 858 patients inadequately controlled on metformin alone, a trial comparing ONGLYZA to placebo in 455 patients inadequately controlled on insulin alone or on insulin in combination with metformin, a trial comparing ONGLYZA to placebo in 257 patients inadequately controlled on metformin plus a sulfonylurea, and a trial comparing ONGLYZA to placebo in 170 patients with type 2 diabetes and moderate or severe renal impairment or ESRD.

14.1 Monotherapy

A total of 766 patients with type 2 diabetes inadequately controlled on diet and exercise (A1C $\geq 7\%$ to $\leq 10\%$) 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. The 10 mg dosage is not an approved dosage. 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 5). 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 5: 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-naïve 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 ($A1C \geq 7\%$ and $\leq 10\%$) 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. 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. The 10 mg dosage is not an approved dosage. 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 6). 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 6: 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)	

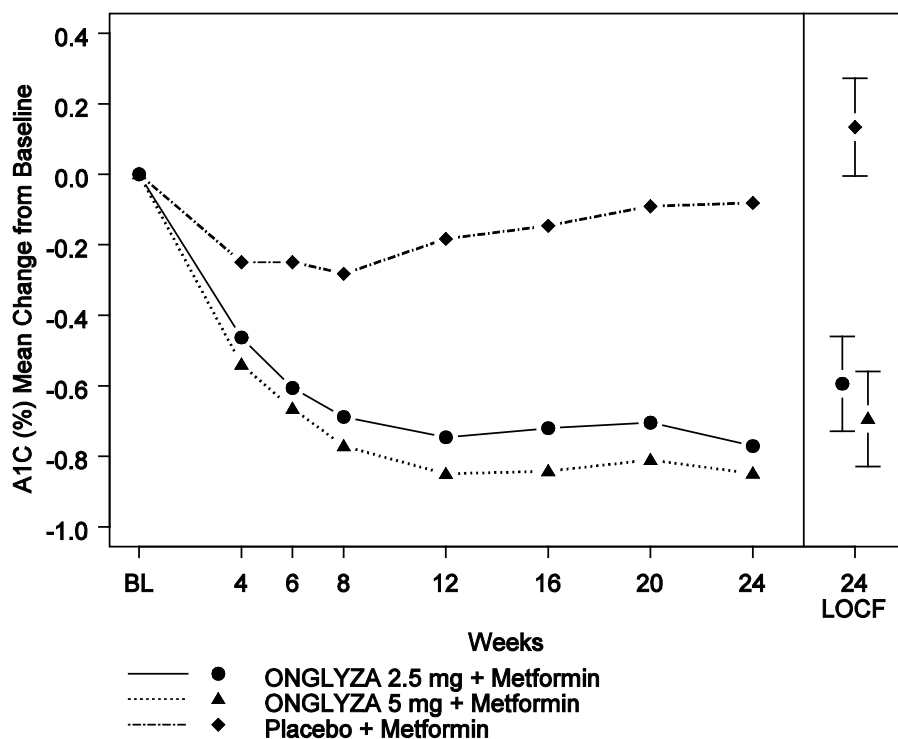
* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

[†] 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 $\geq 7\%$ to $\leq 10.5\%$) 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. 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 7). 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 7: 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 \geq 7.5% to \leq 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 \geq 7% to \leq 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 8). 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 8: 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, active-controlled trial to evaluate the efficacy and safety of ONGLYZA coadministered with metformin in patients with inadequate glycemic control (A1C \geq 8% to \leq 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. The 10 mg dosage is not an approved dosage. 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 9).

Table 9: 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)
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

Add-On Combination Therapy with Metformin versus Glipizide Add-On Combination Therapy with Metformin

In this 52-week, active-controlled trial, a total of 858 patients with type 2 diabetes and inadequate glycemic control (A1C >6.5% and ≤10%) on metformin alone were randomized to double-blind add-on therapy with ONGLYZA or glipizide. Patients were required to be on a stable dose of metformin (at least 1500 mg daily) for at least 8 weeks prior to enrollment.

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 (1500-3000 mg based on their pre-study dose). Following the lead-in period, eligible patients were randomized to 5 mg of ONGLYZA or 5 mg of glipizide in addition to their current dose of open-label metformin. Patients in the glipizide plus metformin group underwent blinded titration of the glipizide dose during the first 18 weeks of the trial up to a maximum glipizide dose of 20 mg per day. Titration was based on a goal FPG ≤110 mg/dL or the highest tolerable glipizide dose. Fifty percent (50%) of the glipizide-treated patients were titrated to the 20-mg daily dose; 21% of the glipizide-treated patients had a final daily glipizide dose of 5 mg or less. The mean final daily dose of glipizide was 15 mg.

After 52 weeks of treatment, ONGLYZA and glipizide resulted in similar mean reductions from baseline in A1C when added to metformin therapy (Table 10). This conclusion may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C <9%).

From a baseline mean body weight of 89 kg, there was a statistically significant mean reduction of 1.1 kg in patients treated with ONGLYZA compared to a mean weight gain of 1.1 kg in patients treated with glipizide (p<0.0001).

Table 10: Glycemic Parameters at Week 52 in an Active-Controlled Trial of ONGLYZA versus Glipizide in Combination with Metformin*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=428	Titrated Glipizide + Metformin N=430
Hemoglobin A1C (%)	N=423	N=423
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean [†])	-0.6	-0.7
Difference from glipizide + metformin (adjusted mean [†])	0.1	
95% Confidence Interval	(-0.02, 0.2) [‡]	
Fasting Plasma Glucose (mg/dL)	N=420	N=420
Baseline (mean)	162	161
Change from baseline (adjusted mean [†])	-9	-16
Difference from glipizide + metformin (adjusted mean [†])	6	
95% Confidence Interval	(2, 11) [§]	

* Intent-to-treat population using last observation on study.

[†] Least squares mean adjusted for baseline value.

[‡] ONGLYZA + metformin is considered non-inferior to glipizide + metformin because the upper limit of this confidence interval is less than the prespecified non-inferiority margin of 0.35%.

[§] Significance not tested.

Add-On Combination Therapy with Insulin (with or without metformin)

A total of 455 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 insulin in patients with inadequate glycemic control (A1C $\geq 7.5\%$ and $\leq 11\%$) on insulin alone (N=141) or on insulin in combination with a stable dose of metformin (N=314). Patients were required to be on a stable dose of insulin (≥ 30 units to ≤ 150 units daily) with $\leq 20\%$ variation in total daily dose for ≥ 8 weeks prior to screening. Patients entered the trial on intermediate- or long-acting (basal) insulin or premixed insulin. Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a premixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, four-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin if applicable) at their pretrial dose(s). Following the lead-in period, eligible patients were randomized to add-on therapy with either ONGLYZA 5 mg or placebo. Doses of the antidiabetic

therapies were to remain stable but patients were rescued and allowed to adjust the insulin regimen if specific glycemic goals were not met or if the investigator learned that the patient had self-increased the insulin dose by >20%. Data after rescue were excluded from the primary efficacy analyses.

Add-on therapy with ONGLYZA 5 mg provided significant improvements from baseline to Week 24 in A1C and PPG compared with add-on placebo (Table 11). Similar mean reductions in A1C versus placebo were observed for patients using ONGLYZA 5 mg add-on to insulin alone and ONGLYZA 5 mg add-on to insulin in combination with metformin (−0.4% and −0.4%, respectively). The percentage of patients who discontinued for lack of glycemic control or who were rescued was 23% in the ONGLYZA group and 32% in the placebo group.

The mean daily insulin dose at baseline was 53 units in patients treated with ONGLYZA 5 mg and 55 units in patients treated with placebo. The mean change from baseline in daily dose of insulin was 2 units for the ONGLYZA 5 mg group and 5 units for the placebo group.

Table 11: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Insulin*

Efficacy Parameter	ONGLYZA 5 mg + Insulin (+/- Metformin) N=304	Placebo + Insulin (+/- Metformin) N=151
Hemoglobin A1C (%)	N=300	N=149
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean [†])	−0.7	−0.3
Difference from placebo (adjusted mean [†])	−0.4 [‡]	
95% Confidence Interval	(−0.6, −0.2)	
2-hour Postprandial Glucose (mg/dL)	N=262	N=129
Baseline (mean)	251	255
Change from baseline (adjusted mean [†])	−27	−4
Difference from placebo (adjusted mean [†])	−23 [§]	
95% Confidence Interval	(−37, −9)	

* Intent-to-treat population using last observation on study or last observation prior to insulin rescue therapy for patients needing rescue.

[†] Least squares mean adjusted for baseline value and metformin use at baseline.

[‡] p-value <0.0001 compared to placebo + insulin

[§] p-value <0.05 compared to placebo + insulin

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 17% (52/300) with ONGLYZA in combination with insulin compared to 7% (10/149) with placebo. Significance was not tested.

Add-On Combination Therapy with Metformin plus Sulfonylurea

A total of 257 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 plus a sulfonylurea in patients with inadequate glycemic control (A1C \geq 7% and \leq 10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose, with minimum dose for enrollment being 1500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrollment being \geq 50% of the maximum recommended dose) for \geq 8 weeks prior to enrollment.

Patients who met eligibility criteria were entered in a 2-week enrollment period to allow assessment of inclusion/exclusion criteria. Following the 2-week enrollment period, eligible patients were randomized to either double-blind ONGLYZA (5 mg once daily) or double-blind matching placebo for 24 weeks. During the 24-week double-blind treatment period, patients were to receive metformin and a sulfonylurea at the same constant dose ascertained during enrollment. Sulfonylurea dose could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. In the absence of hypoglycemia, titration (up or down) of study medication during the treatment period was prohibited.

ONGLYZA in combination with metformin plus a sulfonylurea provided significant improvements in A1C and PPG compared with placebo in combination with metformin plus a sulfonylurea (Table 12). The percentage of patients who discontinued for lack of glycemic control was 6% in the ONGLYZA group and 5% in the placebo group.

Table 12: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	ONGLYZA 5 mg + Metformin plus Sulfonylurea N=129	Placebo + Metformin plus Sulfonylurea N=128
Hemoglobin A1C (%)	N=127	N=127
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean [†])	-0.7	-0.1
Difference from placebo (adjusted mean [†])	-0.7 [‡]	
95% Confidence Interval	(-0.9, -0.5)	
2-hour Postprandial Glucose (mg/dL)	N=115	N=113
Baseline (mean)	268	262
Change from baseline (adjusted mean [†])	-12	5
Difference from placebo (adjusted mean [†])	-17 [§]	
95% Confidence Interval	(-32, -2)	

* Intent-to-treat population using last observation prior to discontinuation.

[†] Least squares mean adjusted for baseline value.

[‡] p-value <0.0001 compared to placebo + metformin plus sulfonylurea

[§] p-value <0.05 compared to placebo + metformin plus sulfonylurea

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 31% (39/127) with ONGLYZA in combination with metformin plus a sulfonylurea compared to 9% (12/127) with placebo. Significance was not tested.

14.3 Renal Impairment

A total of 170 patients participated in a 12-week, randomized, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of ONGLYZA 2.5 mg once daily compared with placebo in patients with type 2 diabetes and moderate (n=90) or severe (n=41) renal impairment or ESRD (n=39). In this trial, 98% of the patients were using background antidiabetic medications (75% were using insulin and 31% were using oral antidiabetic medications, mostly sulfonylureas).

After 12 weeks of treatment, ONGLYZA 2.5 mg provided significant improvement in A1C compared to placebo (Table 13). In the subgroup of patients with ESRD, ONGLYZA and

placebo resulted in comparable reductions in A1C from baseline to Week 12. This finding is inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

After 12 weeks of treatment, the mean change in FPG was -12 mg/dL with ONGLYZA 2.5 mg and -13 mg/dL with placebo. Compared to placebo, the mean change in FPG with ONGLYZA was -12 mg/dL in the subgroup of patients with moderate renal impairment, -4 mg/dL in the subgroup of patients with severe renal impairment, and +44 mg/dL in the subgroup of patients with ESRD. These findings are inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

Table 13: A1C at Week 12 in a Placebo-Controlled Trial of ONGLYZA in Patients with Renal Impairment*

Efficacy Parameter	ONGLYZA 2.5 mg N=85	Placebo N=85
Hemoglobin A1C (%)	N=81	N=83
Baseline (mean)	8.4	8.1
Change from baseline (adjusted mean [†])	-0.9	-0.4
Difference from placebo (adjusted mean [†])	-0.4 [‡]	
95% Confidence Interval	(-0.7, -0.1)	

* Intent-to-treat population using last observation on study.

[†] Least squares mean adjusted for baseline value.

[‡] p-value <0.01 compared to placebo

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 14.

Table 14: 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

Table 14: ONGLYZA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
			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 Bottles of 90	0003-4214-11 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 (Medication Guide).

Medication Guide

Healthcare providers should instruct their patients to read the Medication Guide before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom or if any existing symptom persists or worsens.

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.

Pancreatitis

Patients should be informed that acute pancreatitis has been reported during postmarketing use of ONGLYZA. Before initiating ONGLYZA, patients should be questioned about other risk factors for pancreatitis, such as a history of pancreatitis, alcoholism, gallstones, or hypertriglyceridemia. Patients should also be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute

pancreatitis. Patients should be instructed to promptly discontinue ONGLYZA and contact their healthcare provider if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.1)*].

Hypersensitivity Reactions

Patients should be informed that serious allergic (hypersensitivity) reactions, such as angioedema, anaphylaxis, and exfoliative skin conditions, have been reported during postmarketing use of ONGLYZA. If symptoms of these allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking ONGLYZA and seek medical advice promptly.

Missed Dose

Patients should be informed that if they miss a dose of ONGLYZA they should take the next dose as prescribed, unless otherwise instructed by their healthcare provider. Patients should be instructed not to take an extra dose the next day.

Administration Instructions

Patients should be informed that ONGLYZA tablets must not be split or cut.

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:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

1297954A0 / 1256314A4

MEDICATION GUIDE
ONGLYZA (on-GLY-zah)
(saxagliptin)
tablets

Read this Medication Guide carefully before you start taking ONGLYZA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have any questions about ONGLYZA, ask your healthcare provider.

What is the most important information I should know about ONGLYZA?

Serious side effects can happen to people taking ONGLYZA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking ONGLYZA:

Tell your healthcare provider if you have ever had

- inflammation of your pancreas (pancreatitis)
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

It is not known if having these medical problems will make you more likely to get pancreatitis with ONGLYZA.

Stop taking ONGLYZA and contact your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is ONGLYZA?

- ONGLYZA is a prescription medicine used with diet and exercise to control high blood sugar (hyperglycemia) in adults with type 2 diabetes.

- ONGLYZA lowers blood sugar by helping the body increase the level of insulin after meals.
- ONGLYZA is unlikely by itself to cause your blood sugar to be lowered to a dangerous level (hypoglycemia) because it does not work well when your blood sugar is low. However, hypoglycemia may still occur with ONGLYZA. Your risk for getting hypoglycemia is higher if you take ONGLYZA with some other diabetes medicines, such as a sulfonylurea or insulin.
- ONGLYZA is not for people with type 1 diabetes.
- ONGLYZA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take ONGLYZA.

It is not known if ONGLYZA is safe and effective in children younger than 18 years old.

Who should not take ONGLYZA?

Do not take ONGLYZA if you:

- are allergic to any ingredients in ONGLYZA. See the end of this Medication Guide for a complete list of ingredients in ONGLYZA.

Symptoms of a serious allergic reaction to ONGLYZA may include:

- swelling of your face, lips, throat, and other areas on your skin
- difficulty with swallowing or breathing
- raised, red areas on your skin (hives)
- skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.

What should I tell my healthcare provider before taking ONGLYZA?

Before you take ONGLYZA, tell your healthcare provider if you:

- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if ONGLYZA will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.

- are breast-feeding or plan to breast-feed. ONGLYZA may be passed in your milk to your baby. Talk with your healthcare provider about the best way to feed your baby while you take ONGLYZA.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

ONGLYZA may affect the way other medicines work, and other medicines may affect how ONGLYZA works. Contact your healthcare provider if you will be starting or stopping certain other types of medications, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of ONGLYZA might need to be changed.

How should I take ONGLYZA?

- Take ONGLYZA by mouth one time each day exactly as directed by your healthcare provider. Do not change your dose without talking to your healthcare provider.
- ONGLYZA can be taken with or without food.
- Do not split or cut ONGLYZA tablets.
- During periods of stress on the body, such as:
 - fever
 - trauma
 - infection
 - surgery

Contact your healthcare provider right away as your medication needs may change.

- Your healthcare provider should test your blood to measure how well your kidneys are working before and during your treatment with ONGLYZA. You may need a lower dose of ONGLYZA if your kidneys are not working well.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
- If you miss a dose of ONGLYZA, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your

regular time. Do not take two doses at the same time unless your healthcare provider tells you to do so. Talk to your healthcare provider if you have questions about a missed dose.

- If you take too much ONGLYZA, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of ONGLYZA?

ONGLYZA can cause serious side effects, including:

- See “**What is the most important information I should know about ONGLYZA?**”
- **Allergic (hypersensitivity) reactions**, such as:
 - swelling of your face, lips, throat, and other areas on your skin
 - difficulty with swallowing or breathing
 - raised, red areas on your skin (hives)
 - skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.

Common side effects of ONGLYZA include:

- upper respiratory tract infection
- urinary tract infection
- headache

Low blood sugar (hypoglycemia) may become worse in people who also take another medication to treat diabetes, such as sulfonylureas or insulin. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:

- shaking
- sweating
- rapid heartbeat
- change in vision
- hunger
- headache
- change in mood

Swelling or fluid retention in your hands, feet, or ankles (peripheral edema) may become worse in people who also take a thiazolidinedione to treat diabetes. If you do not know whether you are already on this type of medication, ask your healthcare provider.

These are not all of the possible side effects of ONGLYZA. Tell your healthcare provider if you have any side effects that bother you or that do not go away. For more information, ask your healthcare provider.

Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store ONGLYZA?

Store ONGLYZA between 68°F and 77°F (20°C and 25°C).

Keep ONGLYZA and all medicines out of the reach of children.

General information about the use of ONGLYZA

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use ONGLYZA for a condition for which it was not prescribed. Do not give ONGLYZA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ONGLYZA. If you would like to know more information about ONGLYZA, talk with your healthcare provider. You can ask your healthcare provider for additional information about ONGLYZA that is written for healthcare professionals. For more information, go to www.ONGLYZA.com or call 1-800-ONGLYZA.

What are the ingredients of ONGLYZA?

Active ingredient: saxagliptin

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.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar so that it is as close to normal as possible.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ONGLYZA (saxagliptin) tablets

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

1297954A0 / 1256314A4 / 1296566A1

Rev May 2013