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. (1.1, 14)

Limitation of use:
• Not used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.2)

--------------- DOSAGE AND ADMINISTRATION ---------------

Recommended dosage is 2.5 mg or 5 mg once daily regardless of meals. (2.1)

• Patients eGFR <45 mL/min/1.73 m² (with moderate or severe renal impairment, or end-stage renal disease): 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)

• 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 ---------------

• Pancreatitis: If pancreatitis is suspected, promptly discontinue ONGLYZA. (5.1)

• Heart Failure: Consider the risks and benefits of ONGLYZA in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.2)

• 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. (5.3, 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. (5.4, 6.1, 6.2)

• Arthralgia: Severe and disabling arthralgia has been reported in patients taking DPP4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.5)

• Bullous Pemphigoid: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue ONGLYZA. (5.6)

• Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA. (5.7)

--------------- 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)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2018

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*Sections or subsections omitted from the full prescribing information are not listed.
The dosage of ONGLYZA is 2.5 mg once daily (regardless of meals) for patients and periodically thereafter.

Because the dosage of ONGLYZA should be limited to 2.5 mg based upon renal 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.

The dosage of ONGLYZA is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole, azole antifungal agents, clarithromycin, indinavir, iraconazole, nefazodone, ritonavir, saquinavir, and telithromycin) (see Clinical Pharmacology (12.3) and Clinical Studies (14.2), ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

The dosage of ONGLYZA is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 inhibitors (e.g., ketoconazole, azole antifungal agents, clarithromycin, indinavir, iraconazole, nefazodone, ritonavir, saquinavir, and telithromycin) (see Clinical Pharmacology (12.3) and Clinical Studies (14.2)).

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 (5.3)).

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.

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 (5.4) and Adverse Reactions (6.2)).

WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis in patients taking ONGLYZA. In a cardiovascular outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), cases of definite acute pancreatitis were confirmed in 17 of 8240 (0.2%) patients receiving ONGLYZA compared to 9 of 8270 (0.1%) patients receiving placebo. The incidence of pancreatitis is higher in patients receiving ONGLYZA with a mean duration of exposure to ONGLYZA of 21 weeks. The mean age of these patients was 55 years, 14% were 75 years or older and 48% were male. The population was 67.5% White, 4.6% Black or African American, 17.4% Asian, Other 10.5% and 9.8% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 5.2 years and a mean HbA1c of 8.2%. Baseline estimated renal function was normal or mildly impaired (eGFR=60mL/min/1.73m2) in 91% of these patients.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of ONGLYZA. These adverse reactions occurred more commonly on ONGLYZA than on placebo and occurred in at least 5% of patients treated with ONGLYZA.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>ONGLYZA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Headache</td>
<td>5.9</td>
<td>5.9</td>
</tr>
</tbody>
</table>

* 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 greater than 2% and more commonly than on placebo and at a rate 25% and more commonly than on placebo.

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 patients pooled analysis of 2.5 mg, 5 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, occurred in a single patient in the clinical development program. The relationship of this event to ONGLYZA is not known.

Discontinuation of therapy due to adverse reactions occurred in 2.2%, 3.3%, and 1.8% of subjects receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse reactions (reported in at least 2 subjects treated with ONGLYZA 2.5 mg or at least 2 subjects treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lypohemia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0%), and blood creatinine increased (0.1% and 0% versus 0%), and blood creatinine phosphokinase increased (0.1% and 0.2% versus 0%).

Adverse Reactions with Concomitant Use with Insulin

In the add-on to insulin trial (see Clinical Studies (14.1)), 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)).
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 glimepiride 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 ≤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 (5.5)]. The incidence of reported hypoglycemia for ONGLYZA 2.5 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-naive 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 (accompanied by 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).

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 (accompanied by 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 (5.3)].

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.

Renal Impairment

In the SAVOR trial, adverse reactions related to renal impairment, including laboratory abnormalities (i.e., doubling of serum creatinine compared with baseline and serum creatinine >6 mg/dL) were reported in 5.8% (483/8280) of ONGLYZA-treated patients (3.8%) vs. 4.1% (317/7821) on ONGLYZA and placebo respectively.

The most frequently reported abnormal laboratory test changes (i.e., doubling of serum creatinine compared with baseline and serum creatinine >6 mg/dL) were reported in 5.8% (483/8280) of ONGLYZA-treated patients vs. 4.1% (317/7821) on ONGLYZA and placebo respectively. In the SAVOR trial, mean decreases of approximately 84 cells/microL with ONGLYZA 2.5 mg and 75 cells/microL with ONGLYZA 5 mg 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, 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.

In the SAVOR trial mean decreases of approximately 84 cells/microL with ONGLYZA relative to placebo was observed. The proportion of patients who experienced a decrease in lymphocyte counts to a count of ≤750 cells/microL was 1.6% (156/8280) and 1.0% (78/7821) on ONGLYZA and placebo respectively.

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 post-approval 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 (5.4)].
- Pancreatitis [see Warnings and Precautions (5.1)].
- Severe and disabling arthralgia [see Warnings and Precautions (5.5)].
- Bullous pemphigoid [see Warnings and Precautions (5.6)].

7 DRUG INTERACTIONS

7.1 Strong Inhibitors of CYP3A4/5 Enzymes

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, neflurinav, 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

Risk Summary

Limited data with ONGLYZA in pregnant women are not sufficient to determine a drug-related risk for major birth defects or miscarriages. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see Clinical Considerations].

No adverse developmental effects independent of maternal toxicity were observed when saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis and in pregnant and lactating rats during the pre- and postnatal period [see Data].

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with an HbA1c greater than 7 and has been reported to be as high as 20 to 25% in women with an HbA1c greater than 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preclampsia, spontaneous abortions, preterm birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

In embryo-fetal development studies, saxagliptin was administered to pregnant rats and rabbits during the period of organogenesis, corresponding to the first trimester of human pregnancy. No adverse developmental effects were observed in either species at exposures 150-fold and 152-times the 5 mg clinical dose in rats and rabbits, respectively, based on AUC. Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

In a prenatal and postnatal development study, no adverse developmental effects were observed in maternal rats administered saxagliptin from gestation day 6 through lactation day 21 at exposures up to 470-times the 5 mg clinical dose, based on AUC.

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 2.5 mg and ONGLYZA 5 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, 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.

In the SAVOR trial mean decreases of approximately 84 cells/microL with ONGLYZA relative to placebo was observed. The proportion of patients who experienced a decrease in lymphocyte counts to a count of ≤750 cells/microL was 1.6% (156/8280) and 1.0% (78/7821) on ONGLYZA and placebo respectively.

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.

8.2 Pediatric Use

IN THE PEDIATRIC POPULATION, THE SAFETY AND EFFECTIVENESS OF ONGLYZA HAVE NOT BEEN ESTABLISHED.
8.2 Lactation

Risk Summary

There is no information regarding the presence of ONGLYZA in human milk, the effects on the breastfed infant, or the effects on milk production.

Saxagliptin is present in the milk of lactating rats [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ONGLYZA and any potential adverse effects on the breastfed infant from ONGLYZA or from the underlying maternal condition.

Data

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations.

8.4 Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients under 18 years of age have not been established. Additionally, studies characterizing the pharmacokinetics of ONGLYZA in pediatric patients have not been performed.

8.5 Geriatric Use

In the seven, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, a total of 4751 (42.0%) of the 11301 patients randomized to ONGLYZA were 65 years and over, and 1210 (10.7%) were 75 years and over. No small differences in safety or effectiveness were observed between subjects ≥65 years old and younger subjects. 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)].

8.6 Renal Impairment

In a 12-week randomized placebo-controlled trial, ONGLYZA 2.5 mg was administered to 85 subjects with moderate (n=48) or severe (n=18) renal impairment or end-stage renal disease (ESRD) (n=19) [see Clinical Studies (14)]. The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo. The overall incidence of reported hypoglycemia was 20% among subjects treated with ONGLYZA 2.5 mg and 22% among subjects treated with placebo. Four ONGLYZA-treated subjects (4.7%) and three placebo-treated subjects (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤50 mg/dL).

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 (1S,3S,5S)-2-[(2S)-2-Amino-2-[3-hydroxytricyclo[3.3.1.1(7-9)]dec-1-yl]acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile monohydrate. The empirical formula is C_{24}H_{28}N_{2}O_{6}•H_{2}O and the molecular weight is 333.43. The structural formula is:

![Structural formula of saxagliptin monohydrate](image)

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin or 5.58 mg saxagliptin (3-carbonitrile, monohydrate or (1S,3S,5S)-2-[(2S)-2-Amino-2-[3-hydroxytricyclo[3.3.1.1(7-9)]dec-1-yl]acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin (anhydrous) equivalent to 5 mg saxagliptin and the molecular weight is 333.43. The structural formula is:

![Structural formula of saxagliptin](image)

8.2 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.

12.2 Pharmacodynamics

Cardiac Electrophysiologoy

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 (6 times the MRHD).

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 Cmax 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 Cmax values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and Cmax 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\(_{\text{max}}\)) 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\(_{\text{max}}\) 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 (7.1)].

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of SAX-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\(_{\text{1/2}}\)) 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 compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. The degree of renal impairment did not affect C\(_{\text{max}}\) of saxagliptin or its metabolite. In subjects with moderate renal impairment with eGFR 30 to less than 45 mL/min/1.73m\(^2\), severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m\(^2\)) and ESRD patient on hemodialysis, the AUC values of saxagliptin or its active metabolite were >2 fold higher than AUC values in subjects with normal renal function.

Hepatic Impairment

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C\(_{\text{max}}\) 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 10 mg dosage is not an approved dosage. The corresponding C\(_{\text{max}}\) 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.

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 females, males had approximately 25% higher estimated peak plasma concentrations of 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 Cₚ 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.

**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 Interaction Studies**

**In Vitro Assessment of Drug Interactions**
The metabolism of saxagliptin is primarily mediated by CYP3A4/5. 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.

**In Vivo Assessment of Drug Interactions**

### Table 2: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dosage of Coadministered Drug</th>
<th>Dosage of Saxagliptin</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug)</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1000 mg</td>
<td>100 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 0.98 0.99</td>
<td>saxagliptin 5-hydroxy saxagliptin 0.98 0.99</td>
</tr>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.08 ND</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.08 ND</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10 mg single dose</td>
<td>5 mg single dose</td>
<td>saxagliptin 5-hydroxy saxagliptin 14% 19%</td>
<td>saxagliptin 5-hydroxy saxagliptin 14% 19%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>45 mg QD for 10 days</td>
<td>10 mg QD for 5 days</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.11 ND</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.11 ND</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg q6h first day followed by q12h second day followed by QD for 5 days</td>
<td>10 mg QD for 7 days</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.05 1.06</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.05 1.06</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg QD for 8 days</td>
<td>10 mg QD for 4 days</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.12 1.02</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.12 1.02</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>360 mg LA QD for 9 days</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 2.09 0.66</td>
<td>saxagliptin 5-hydroxy saxagliptin 2.09 0.66</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg QD for 6 days</td>
<td>5 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 0.24 1.03</td>
<td>saxagliptin 5-hydroxy saxagliptin 0.24 1.03</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>40 mg QD for 5 days</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.13 ND</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.13 ND</td>
</tr>
<tr>
<td>Aluminum hydroxide + magnesium hydroxide + simethicone</td>
<td>2400 mg magnesium hydroxide: 2000 mg simethicone: 240 mg</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 0.97 ND</td>
<td>saxagliptin 5-hydroxy saxagliptin 0.97 ND</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.03 ND</td>
<td>saxagliptin 5-hydroxy saxagliptin 1.03 ND</td>
</tr>
</tbody>
</table>

### Limit ONGLYZA dose to 2.5 mg once daily when coadministered with strong CYP3A4/5 inhibitors [see Drug Interactions (7.1) and Dosage and Administration (2.3)]:

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dosage of Coadministered Drug</th>
<th>Dosage of Saxagliptin</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug)</th>
<th>Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>200 mg BID for 9 days</td>
<td>100 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin 2.45 0.12</td>
<td>saxagliptin 5-hydroxy saxagliptin 2.45 0.12</td>
</tr>
</tbody>
</table>

### No dosing adjustments required for the following:

- Metformin 1000 mg 100 mg
- Glyburide 5 mg 10 mg
- Pioglitazone 45 mg QD for 10 days
- Simvastatin 40 mg QD for 8 days
- Diltiazem 360 mg LA QD for 9 days

### No dosing adjustments required for the following:

- Simvastatin 40 mg QD for 8 days
- Diltiazem 360 mg LA QD for 9 days
- Ethinyl estradiol and Norgestimete 5 mg QD for 2 days

### No dosing adjustments required for the following:

- Metformin 1000 mg 100 mg
- Glyburide 5 mg 10 mg
- Pioglitazone 45 mg QD for 10 days
- Simvastatin 40 mg QD for 8 days
- Diltiazem 360 mg LA QD for 9 days
- Ethinyl estradiol and Norgestimete 5 mg QD for 2 days

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**13 NONCLINICAL TOXICOLOGY**

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**
Carcinogenicity was evaluated in 2-year studies conducted in CD-1 mice and Sprague-Dawley rats. Saxagliptin did not increase the incidence of tumors in mice dosed orally at 50, 250, and 600 mg/kg up to 870-times (males) and 1165-times (females) the 5 mg/day clinical dose, based on AUC. Saxagliptin did not increase the incidence of tumors in rats dosed orally at 25, 75, 150, and 300 mg/kg up to 355-times (males) and 2217-times (females) the 5 mg/day clinical dose, based on AUC.

**Mutagenesis**
Saxagliptin was not mutagenic or clastogenic in a battery of genotoxicity tests (Ames bacterial mutagenesis, human and rat lymphocyte cytogenetics, rat bone marrow micronucleus and DNA repair assays). The active metabolite of saxagliptin was not mutagenic in an Ames bacterial assay.

**Impairment of Fertility**
Saxagliptin administered to rats had no effect on fertility or the ability to maintain a litter at exposures up to 603-times and 776-times the 5 mg clinical dose in males and females, based on AUC.

### 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 within exposure approximately 20-times the 5 mg clinical dose, 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 5 mg clinical dose. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.
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 an ONGLYZA dose of 10 mg daily. The 10 mg daily dose of ONGLYZA 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 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.

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. 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 4). 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 4: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA Monotherapy in Patients with Type 2 Diabetes*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 2.5 mg (N=102)</th>
<th>ONGLYZA 5 mg (N=106)</th>
<th>Placebo (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1C (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.9</td>
<td>8.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.4</td>
<td>-0.5</td>
<td>+0.2</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>-0.6†</td>
<td>-0.6†</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval (−0.9, −0.3)</td>
<td>(−0.9, −0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving A1C &lt;7%</td>
<td>35% (35/100)</td>
<td>38%† (38/100)</td>
<td>24% (22/92)</td>
</tr>
</tbody>
</table>

### Fasting Plasma Glucose (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>N=101</th>
<th>N=105</th>
<th>N=92</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>178</td>
<td>171</td>
<td>172</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-15</td>
<td>-9</td>
<td>+6</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>-2†</td>
<td>-15†</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval (−31, −10)</td>
<td>(−25, −4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2-hour Postprandial Glucose (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>N=78</th>
<th>N=84</th>
<th>N=71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>279</td>
<td>278</td>
<td>283</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-45</td>
<td>-43</td>
<td>-6</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>-39†</td>
<td>-37†</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval (−61, −16)</td>
<td>(−59, −15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. A1C; 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%).

### Combination Therapy

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. 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 5). 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.
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. 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 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 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Glyburide*

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 2.5 mg</th>
<th>ONGLYZA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>hemoglobin A1C (%)</td>
<td>N=246</td>
<td>N=250</td>
<td>N=264</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.4</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−0.5 −0.6</td>
<td>+0.1</td>
<td></td>
</tr>
<tr>
<td>Difference from up-titrated glyburide (adjusted mean)</td>
<td>−0.6  −0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−0.8, −0.5)</td>
<td>(−0.9, −0.6)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving A1C &lt;7%</td>
<td>22% 5 (55/246)</td>
<td>23% 6 (57/250)</td>
<td>9% (24/264)</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>N=247</td>
<td>N=252</td>
<td>N=265</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>170</td>
<td>175</td>
<td>174</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−7 −10</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Difference from up-titrated glyburide (adjusted mean)</td>
<td>−8 −10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−14, −1)</td>
<td>(−17, −4)</td>
<td></td>
</tr>
<tr>
<td>2-hour Postprandial Glucose (mg/dL)</td>
<td>N=195</td>
<td>N=202</td>
<td>N=206</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>290</td>
<td>315</td>
<td>323</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−31 −34</td>
<td>+6</td>
<td></td>
</tr>
<tr>
<td>Difference from up-titrated glyburide (adjusted mean)</td>
<td>−38 −42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−50, −27)</td>
<td>(−53, −31)</td>
<td></td>
</tr>
</tbody>
</table>

*Includes patients with a baseline and week 24 value.

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 7). 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 a Thiazolidinedione*

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

*Includes patients with a baseline and week 24 value.

†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 Metformin

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 ≥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. The 10 mg saxagliptin 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

COadminstration 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 ≥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. The 10 mg saxagliptin 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.

Add-On Combination Therapy with Metformin

Add-On Combination Therapy with Metformin in Treatment-Naive Patients

Table 8: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
<td>Metformin</td>
</tr>
<tr>
<td></td>
<td>N=320</td>
<td>N=328</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>N=306</td>
<td>N=313</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−2.5</td>
<td>−2.0</td>
</tr>
<tr>
<td>Difference from placebo + metformin (adjusted mean)</td>
<td>−0.5†</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−0.7, −0.4)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving A1C &lt;7%</td>
<td>60%† (185/307)</td>
<td>41% (129/314)</td>
</tr>
</tbody>
</table>

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)

2-hour Postprandial Glucose (mg/dL) N=320 N=328

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)

Add-On Combination Therapy with Glipizide

Add-On Combination Therapy with Metformin and Glipizide

Add-On Combination Therapy with Glipizide

Add-On Combination Therapy with Glipizide in Combination with Metformin

Table 9: Glycemic Parameters at Week 52 in an Active-Controlled Trial of ONGLYZA versus Glipizide in Combination with Metformin

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 5 mg</th>
<th>Titrated Glipizide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
<td>Metformin</td>
</tr>
<tr>
<td></td>
<td>N=428</td>
<td>N=430</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>N=423</td>
<td>N=423</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−0.6</td>
<td>−0.7</td>
</tr>
<tr>
<td>Difference from glipizide + metformin (adjusted mean)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−0.02, 0.2)†</td>
<td></td>
</tr>
</tbody>
</table>

Add-On Combination Therapy with Metformin plus Sulfonylurea

Add-On Combination Therapy with Metformin plus Sulfonylurea

Add-On Combination Therapy with Metformin versus Placebo

Add-On Combination Therapy with Glipizide versus Placebo
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 combination in placebo with metformin plus a sulfonylurea (Table 11). The percentage of patients who discontinued for lack of glycemic control was 6% in the ONGLYZA group and 5% in the placebo group.

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin plus Sulfonylurea</td>
<td>N=129</td>
<td>N=128</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>N=127</td>
<td>N=127</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.4</td>
<td>8.2</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>–0.7</td>
<td>–0.1</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>–0.7</td>
<td>–0.1</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(–0.9, –0.5)</td>
<td>(–0.9, –0.5)</td>
</tr>
</tbody>
</table>

The group treated with add-on ONGLYZA had statistically significant greater reductions in HbA1c from baseline versus the group treated with placebo (see Table 12).

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.

Add-on Combination Therapy with Metformin plus an SGLT2 Inhibitor

A total of 315 patients with type 2 diabetes participated in this 24-week randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA added to dapagliflozin (an SGLT2 inhibitor) and metformin in patients with a baseline of HbA1c ≥7% to ≤10.5%. The mean age of these subjects was 54.6 years, 1.6% were Black, 6.1% were Asian, 4.1% were Hispanic, and 1.6% were Other race. At baseline the population had diabetes for an average of 7.7 years and a mean HbA1c of 7.9%. The mean eGFR at baseline was 93.4 mL/min/1.73 m². Patients were required to be on a stable dose of metformin (≥1500 mg per day) for at least 8 weeks prior to enrollment. Eligible subjects who completed the screening period entered the lead in treatment period, which included open-label metformin and 15 mg dapagliflozin treatment. Following the lead-in period, eligible patients were randomized to ONGLYZA 5 mg (N=153) or placebo (N=162).

The group treated with add-on ONGLYZA had statistically significant greater reductions in HbA1c from baseline versus the group treated with placebo (see Table 12).

### Table 12: HbA1c Change from Baseline at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-on Combination Therapy with Metformin plus Sulfonylurea

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin plus Sulfonylurea</td>
<td>N=153</td>
<td>N=162</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>–0.5</td>
<td>–0.2</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(–0.6, –0.4)</td>
<td>(–0.3, –0.1)</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>–0.4</td>
<td>–0.4</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(–0.5, –0.2)</td>
<td>(–0.5, –0.2)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 2.5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin plus Sulfonylurea</td>
<td>N=85</td>
<td>N=85</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>–0.9</td>
<td>–0.4</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>–0.4</td>
<td>–0.4</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(–0.7, –0.1)</td>
<td>(–0.7, –0.1)</td>
</tr>
</tbody>
</table>

### 14.3 Cardiovascular Safety Trial

The cardiovascular risk of ONGLYZA was evaluated in SAVOR, a multicenter, multinational, randomized, double-blind study comparing ONGLYZA (N=8280) to placebo (N=8212), both administered in combination with standard of care, in adult patients with type 2 diabetes at high risk for atherosclerotic cardiovascular disease. Of the randomized study subjects, 97.5% completed the trial, and the median duration of follow-up was approximately 2 years. The trial was event-driven, and patients were followed until a sufficient number of events were accrued.

Subjects were at least 40 years of age, had A1C >6.5%, and multiple risk factors (21% of randomized subjects) for cardiovascular disease (age ≥55 years or ≥60 years for women plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking) or established (79% of the randomized subjects) cardiovascular disease defined as a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of cardiovascular disease medications was also balanced (ACE inhibitors or angiotensin receptor blockers [ARBs] 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antplatelet medications 24%).

The majority of subjects were male (67%) and Caucasian (75%) with a mean age of 65 years. Approximately 16% of the population had moderate (estimated glomerular filtration rate [eGFR] ≤60 mL/min/1.73 m²) renal impairment, and 13% had a prior history of heart failure. Subjects had a median duration of type 2 diabetes mellitus of approximately 10 years, and a mean baseline A1C level of 8.0%. Approximately 5% of subjects were treated with diet and exercise only at baseline. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of cardiovascular disease medications was also balanced (ACE inhibitors or ARBs 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antplatelet medications 24%).

The primary analysis in SAVOR was time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event in SAVOR was defined as a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal ischemic stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE and was also powered for a superiority comparison if non-inferiority was demonstrated.

The results of SAVOR, including the contribution of each component to the primary composite endpoint, are shown in Table 14. The incidence rate of MACE was similar in both treatment arms: 3.8 MACE per 100 patient-years on placebo vs. 3.8 MACE per 100 patient-years on ONGLYZA. The estimated hazard ratio of MACE associated with ONGLYZA relative to placebo was 1.00 with a 95.1% confidence interval of (0.89, 1.12). The upper bound of this confidence interval, 1.12, excluded a risk margin larger than 1.3.
Vital status was obtained for 99% of subjects in the trial. There were 798 deaths in the placebo group (4.6%). The risk of deaths from all cause (Table 15) was not statistically different for ONGLYZA and the placebo arm. Numerically more patients (5.1%) died in the ONGLYZA group than in the placebo group (4.6%). The risk of deaths from all cause (Table 15) was not statistically different for ONGLYZA and the placebo arm. Numerically more patients (5.1%) died in the ONGLYZA group than in the placebo group (4.6%).

Table 15: All-cause mortality by Treatment Group in the SAVOR Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Subjects (%)</th>
<th>Rate per 100 PY</th>
<th>Number of Subjects (%)</th>
<th>Rate per 100 PY</th>
<th>Hazard Ratio (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONGLYZA</td>
<td>N=8280 Total PY = 16308.8</td>
<td>3.8</td>
<td>N=8212 Total PY = 16156.0</td>
<td>3.8</td>
<td>1.00 (0.89, 1.12)</td>
</tr>
<tr>
<td>CV death</td>
<td>813 (7.4)</td>
<td>3.8</td>
<td>609 (7.4)</td>
<td>3.8</td>
<td>1.00 (0.89, 1.12)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>245 (3.0)</td>
<td>1.5</td>
<td>234 (2.8)</td>
<td>1.4</td>
<td>1.00 (0.89, 1.12)</td>
</tr>
<tr>
<td>Non-fatal ischemic stroke</td>
<td>233 (2.8)</td>
<td>1.4</td>
<td>260 (3.2)</td>
<td>1.6</td>
<td>1.00 (0.89, 1.12)</td>
</tr>
<tr>
<td>Total</td>
<td>135 (1.6)</td>
<td>0.8</td>
<td>115 (1.4)</td>
<td>0.7</td>
<td>1.00 (0.89, 1.12)</td>
</tr>
</tbody>
</table>

The Kaplan-Meier-based cumulative event probability is presented in Figure 2 for time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for both ONGLYZA and placebo arms are close together throughout the duration of the trial. The estimated cumulative event probability is approximately linear for both arms, indicating that the incidence of MACE for both arms was constant over the trial duration.

Figure 2: Cumulative Percent of Time to First MACE

Vital status was obtained for 99% of subjects in the trial. There were 798 deaths in the SAVOR trial. Numerically more patients (5.1%) died in the ONGLYZA group than in the placebo group (4.6%). The risk of deaths from all cause (Table 15) was not statistically different between the treatment groups (HR: 1.11; 95.1% CI: 0.96, 1.27).

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 16.
What is the most important information I should know about ONGLYZA?

Serious side effects can happen to people taking ONGLYZA, including:

1) 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)
- a history of alcoholism

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.

2) Heart failure. Heart failure means your heart does not pump blood well enough.

**Before you start taking ONGLYZA:**

Tell your healthcare provider if you

- have ever had heart failure or have problems with your kidneys.

Contact your healthcare provider right away if you have any of the following symptoms:

- increasing shortness of breath or trouble breathing, especially when you lie down
- swelling or fluid retention, especially in the feet, ankles or legs

These may be symptoms of heart failure.

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).

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
- raised, red areas on your skin (hives)
- difficulty with swallowing or breathing
- skin rash, itching, flaking, or peeling

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

Before taking ONGLYZA, tell your healthcare provider about all of your medical conditions, including 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 over-the-counter 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, or 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 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.
• Joint pain. Some people who take medicines called DPP-4 inhibitors like ONGLYZA, may develop joint pain that can be severe. Call your healthcare provider if you have severe joint pain.
• Skin reaction. Some people who take medicines called DPP-4 inhibitors, like ONGLYZA, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your healthcare provider right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking ONGLYZA.

Common side effects of ONGLYZA include:
• upper respiratory tract infection
• urinary tract infection
• headache
• low blood sugar (hypoglycemia)

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.

Call your doctor 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 to 77°F (20°C to 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. You can ask your healthcare provider for additional information about ONGLYZA that is written for health professionals.

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.

ONGLYZA is a registered trademark of the AstraZeneca group of companies. Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850.
For more information, go to www.ONGLYZA.com or call 1-800-ONGLYZA.