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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

ONGLYZA® (saxagliptin) tablets, for oral use

Initial U.S. Approval: 2009

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)

Recommended dosage is 2.5 mg or 5 mg once daily taken 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)

Dosage forms and strengths:

• Tablets: 5 mg and 2.5 mg. (3)

• 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)

• Hyposensitivity-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)

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

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: 6/2019

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® 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)

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

Recommended dosage is 2.5 mg or 5 mg once daily taken 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)

Dosage forms and strengths:

• Tablets: 5 mg and 2.5 mg. (3)

• 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)

• Hyposensitivity-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)

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

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: 6/2019
The dosage of ONGLYZA is 2.5 mg once daily (regardless of meals) for patients with eGFR <45mL/min/1.73 m² (which includes a subset of moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis) [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.

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.

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, neflinavir, ritonavir, saquinavir, and telithromycin) [see Drug Interactions (7.1) and Clinical Pharmacology (12.7)]

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 (5.3)].

3 DOSAGE FORMS AND STRENGTHS

- ONGLYZA (saaxaglin) 5 mg tablets are pink, biconvex, round, film-coated tablets with “5” printed on one side and “215” printed on the reverse side, in blue ink.
- ONGLYZA (saaxaglin) 2.5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with “2.5” printed on one side and “2412” 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 (5.4) and Adverse Reactions (6.2)].

5 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 8173 (0.1%) receiving placebo. Prevalence risk factors for pancreatitis were identified in 88% (1572) of those patients receiving ONGLYZA and in 100% (9/9) of those patients receiving placebo.

After initiation of ONGLYZA, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue ONGLYZA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ONGLYZA.

5.2 Heart Failure

In a cardiovascular outcomes trial enrolling participants with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to ONGLYZA (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of hospitalization for heart failure was higher in the ONGLYZA group (estimated Hazard Ratio: 1.27; 95% CI: 1.07, 1.51). Subjects with a prior history of heart failure and subjects with renal impairment had a higher risk for hospitalization for heart failure, irrespective of treatment assignment.

Consider the risks and benefits of ONGLYZA prior to initiating treatment in patients at a higher risk for heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of ONGLYZA.

5.3 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)].

5.4 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 (DPP-4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with ONGLYZA.

5.5 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.6 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving ONGLYZA. If bullous pemphigoid is suspected, ONGLYZA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Pancreatitis [see Warnings and Precautions (5.1)]
- Heart Failure [see Warnings and Precautions (5.2)]
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin [see Warnings and Precautions (5.3)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.4)]
- Severe and disabling arthralgia [see Warnings and Precautions (5.5)]
- Bullous pemphigoid [see Warnings and Precautions (5.6)]

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 in Efficacy Trials

The data in Table 1 are derived from a pool of 5 placebo-controlled clinical trials [see Clinical Studies (14)]. These data shown in the table reflect exposure of 802 patients to ONGLYZA and a mean duration of exposure to ONGLYZA of 21 weeks. The mean age of these patients was 55 years, 1.4% were 75 years or older and 48.4% were female. The population baseline 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>% of Patients</th>
<th>ONGLYZA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=882</td>
<td>8173</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Headache</td>
<td>6.5</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 changes.

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

In 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 0% 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.

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 hypomania (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 3.2% versus 0%).

Adverse Reactions with Concomitant Use with Insulin

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 fingertip 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 (5.3)]. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg was higher, 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% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingertip 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 (accompanying fingertip blood glucose ≤50 mg/dL) was higher with ONGLYZA 5 mg (5.3%) versus placebo (0.5%).

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 changes (i.e., doubling of serum creatinine compared with baseline and serum creatinine >2.5 mg/dL) reported in none of the ONGLYZA-treated patients and in 35 glipizide-treated patients (8.1%) versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia was associated with ONGLYZA use.

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 2968 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 14 to 129 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.

Absolutes 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/μL, mean decreases of approximately 100 and 120 cells/μL with ONGLYZA 2.5 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/μL 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.

In the SAVOR trial mean decreases of approximately 84 cells/μL with ONGLYZA relative to placebo was observed. The proportion of patients who experienced a decrease in lymphocyte counts to a count of ≤750 cells/μL was 1.6% (136/8280) and 1.0% (78/8212) 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
- Pancreatitis
- Severe and disabling arthralgia
- Bullous pemphigoid
- Rhabdomyolysis

7 DRUG INTERACTIONS
7.1 Strong Inhibitors of CYP3A4/5 Enzymes
Ketconazole 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, neflunin, 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-associated 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 embryofetal risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data
Animal Data
In embryofetal 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- and 152-times the 5 mg clinical dose in rats and rabbits, respectively, based on AUC. Saxagliptin decreases the plasma 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.
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 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 12% (1317) were 75 years and over. No overall 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).

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-[(3-hydroxytricyclo[3.3.1.1\(^3,7\) ]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is \(\text{C}_{18}\text{H}_{25}\text{N}_{3}\text{O}_{2}\cdot\text{H}_{2}\text{O}\) and the molecular weight is 333.43. The structural formula is:

\[
\text{HO} \quad \text{NH} \quad \text{CN} \\
\text{H}_{2}\text{N} \quad \text{O} \quad \text{H}_{2}\text{O} \\
\text{H}_{2}\text{N} \quad \text{O} \quad \text{H}_{2}\text{O}
\]

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

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg 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)].
Geriatric
No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C\textsubscript{\text{AUC}} 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 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 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>AUC†</th>
<th>C\textsubscript{\text{max}}</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dosing adjustments required for the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>1000 mg</td>
<td>100 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>0.98</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.99</td>
<td>0.88</td>
</tr>
<tr>
<td>Glyburide</td>
<td>5 mg</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>0.98</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>1.08</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10 mg single dose</td>
<td>5 mg single dose</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14%</td>
<td>16%</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</td>
<td>1.11</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.11</td>
<td>ND</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg q6h first day</td>
<td>10 mg QD for 5 days</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>1.05</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>followed by q12h second day</td>
<td></td>
<td></td>
<td>1.06</td>
<td>1.02</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</td>
<td>1.12</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.02</td>
<td>1.08</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>360 mg LA QD for 9 days</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>2.09</td>
<td>1.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.66</td>
<td>0.57</td>
</tr>
<tr>
<td>Rifampin†</td>
<td>600 mg QD for 6 days</td>
<td>5 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>0.24</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.03</td>
<td>1.39</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>40 mg QD for 5 days</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>1.13</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND</td>
<td>0.98</td>
</tr>
<tr>
<td>Aluminum hydroxide + magnesium hydroxide + simethicone</td>
<td>2400 mg hydroxide: 2400 mg magnesium hydroxide: 2400 mg simethicone: 240 mg</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>0.97</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
<td>ND</td>
</tr>
<tr>
<td>Famotidine</td>
<td>40 mg</td>
<td>10 mg</td>
<td>saxagliptin 5-hydroxy saxagliptin</td>
<td>1.03</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.14</td>
<td>ND</td>
</tr>
</tbody>
</table>

Table 2: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin (cont’d)

| Coadministered Drug | Dosage of Coadministered Drug* | Dosage of Saxagliptin* | Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00 |
|---------------------|-------------------------------|-----------------------|---------------------------------------------------------------|------|----------|
| No dosing adjustments required for the following: | | | | | |
| Metformin           | 1000 mg                       | 100 mg                | saxagliptin 5-hydroxy saxagliptin                           | 2.45 | 0.12     |
| Glyburide           | 5 mg                          | 10 mg                 | saxagliptin 5-hydroxy saxagliptin                           | 1.62 |
| Pioglitazone†       | 45 mg QD for 10 days          | 10 mg QD for 5 days   | saxagliptin 5-hydroxy saxagliptin                           | 2.44 |
| Simvastatin         | 40 mg QD for 8 days           | 10 mg QD for 4 days   | simvastatin simvastatin acid                                | 1.14 |
| Diltiazem           | 360 mg LA QD for 9 days       | 10 mg                 | diltiazem                                                   | 1.10 |
| Ketoconazole        | 200 mg BID for 9 days         | 100 mg                | ketoconazole                                                | 0.87 |

Table 3: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs

| Coadministered Drug | Dosage of Coadministered Drug* | Dosage of Saxagliptin* | Geometric Mean Ratio (ratio with/without saxagliptin) No Effect = 1.00 |
|---------------------|-------------------------------|-----------------------|---------------------------------------------------------------|------|----------|
| No dosing adjustments required for the following: | | | | | |
| Metformin           | 1000 mg                       | 100 mg                | metformin                                                   | 1.20 |
| Glyburide           | 5 mg                          | 10 mg                 | glyburide                                                   | 1.06 |
| Pioglitazone†       | 45 mg QD for 10 days          | 10 mg QD for 5 days   | pioglitazone hydroxy-pioglitazone                            | 1.08 |
| Simvastatin         | 40 mg QD for 8 days           | 10 mg QD for 4 days   | simvastatin simvastatin acid                                | 1.16 |
| Diltiazem           | 360 mg LA QD for 9 days       | 10 mg                 | diltiazem                                                   | 1.10 |
| Ketoconazole        | 200 mg BID for 9 days         | 100 mg                | ketoconazole                                                | 0.87 |

* Single dose unless otherwise noted. The 10 mg saxagliptin dose is not an approved dosage.
† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses
‡ ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting

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.
14 CLINICAL STUDIES

14.1 Glycemic Efficacy Trials

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. At least one of these trials also evaluated 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 has also been evaluated in five 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, a trial comparing ONGLYZA to placebo in 315 patients inadequately controlled on dapagliflozin and metformin, and a trial comparing ONGLYZA to placebo in 170 patients with type 2 diabetes and moderate or severe renal impairment or ESRD.

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. ONGLYZA effectiveness was evaluated at the last measurement prior to rescue therapy for patients needing rescue. Dose titration of ONGLYZA was not permitted.

In these six, double-blind trials, ONGLYZA was evaluated at doses of 2.5 mg and 5 mg once daily. At least one of these trials also evaluated 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.

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 failed to meet specific 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</th>
<th>ONGLYZA 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>N=100 N=102</td>
<td>N=103 N=106</td>
<td>N=95</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.9 8.0</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−0.4 −0.5</td>
<td>+0.2</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>−0.6 −0.6</td>
<td>−0.6</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−0.9, −0.3)</td>
<td>(−0.9, −0.4)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving A1C &lt;7%</td>
<td>35% (35/100)</td>
<td>38% (38/103)</td>
<td>24% (22/92)</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>N=101 N=102</td>
<td>N=105 N=106</td>
<td>N=92</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>178 171</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−15 −9</td>
<td>+6</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>−21 −15</td>
<td>−21</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−31, −10)</td>
<td>(−25, −4)</td>
<td></td>
</tr>
<tr>
<td>2-hour Postprandial Glucose (mg/dL)</td>
<td>N=78 N=84</td>
<td>N=84 N=71</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>279 278</td>
<td>283</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−45 −43</td>
<td>−6</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>−39 −37</td>
<td>−39</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−61, −16)</td>
<td>(−59, −15)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>ONGLYZA 2.5 mg + Metformin</th>
<th>ONGLYZA 5 mg + Metformin</th>
<th>Placebo + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>N=186 N=192</td>
<td>N=186 N=191</td>
<td>N=179</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.1 8.1</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−0.6 −0.7</td>
<td>−0.6 −0.7</td>
<td>+0.1</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>−0.7 −0.8</td>
<td>+0.1</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−0.9, −0.5)</td>
<td>(−1.0, −0.6)</td>
<td></td>
</tr>
<tr>
<td>Percent of patients achieving A1C &lt;7%</td>
<td>37% (69/186)</td>
<td>44% (81/186)</td>
<td>17% (29/175)</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>N=188 N=187</td>
<td>N=176</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>174 179</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−14 −22</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>−16 −23</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−23, −9)</td>
<td>(−30, −16)</td>
<td></td>
</tr>
<tr>
<td>2-hour Postprandial Glucose (mg/dL)</td>
<td>N=155 N=155</td>
<td>N=135</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>294 296</td>
<td>295</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−62 −58</td>
<td>−18</td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>−44 −50</td>
<td>−24</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−60, −27)</td>
<td>(−56, −24)</td>
<td></td>
</tr>
</tbody>
</table>

a Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue
b Least squares mean adjusted for baseline value
c p-value <0.0001 compared to placebo + metformin
d p-value <0.05 compared to placebo + metformin

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

* Treatment with either ONGLYZA 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of −0.4% and −0.3%, respectively). Treatment with ONGLYZA 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of −0.4%).
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%) 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 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 pre-specified 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 N=248</th>
<th>ONGLYZA 5 mg N=253</th>
<th>Placebo N=267</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin A1C (%)</strong></td>
<td></td>
<td></td>
<td></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</td>
<td>−0.6</td>
<td>+0.1</td>
</tr>
<tr>
<td><strong>95% Confidence Interval</strong></td>
<td>(−0.9, −0.6)</td>
<td>(−0.9, −0.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Percent of patients achieving A1C &lt;7%</strong></td>
<td>22%§ (55/248)</td>
<td>23%§ (57/250)</td>
<td>9% (24/264)</td>
</tr>
</tbody>
</table>

### 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 N=196</th>
<th>ONGLYZA 5 mg N=202</th>
<th>Placebo N=206</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin A1C (%)</strong></td>
<td></td>
<td></td>
<td></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</td>
<td>−0.6</td>
<td>+0.1</td>
</tr>
<tr>
<td><strong>95% Confidence Interval</strong></td>
<td>(−0.9, −0.6)</td>
<td>(−0.9, −0.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Percent of patients achieving A1C &lt;7%</strong></td>
<td>22%§ (55/248)</td>
<td>23%§ (57/250)</td>
<td>9% (24/264)</td>
</tr>
</tbody>
</table>

*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 Metformin in Treatment-Naïve Patients

A total of 1306 treatment-naïve 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 ≥7% to ≤10%) on diet and exercise alone. Patients were required to be treatment-naïve 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 (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 ≥7.5% and ≤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 ≥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 were 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 10). 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.

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 ≥7% and ≤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 ≥50% of the maximum recommended dose) for ≥8 weeks prior to enrollment.

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 not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant.

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 ≥7% and ≤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 ≥50% of the maximum recommended dose) for ≥8 weeks prior to enrollment.

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Add-On Combination Therapy with Metformin plus Sulfonylurea

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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 not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant. The percent of patients achieving an A1C <7% was not statistically significant.
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 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 11: Glycemic Parameters 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=129</td>
<td>N=127</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>Baseline (mean)</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Change from baseline (adjusted mean)</td>
<td>−0.7</td>
</tr>
<tr>
<td></td>
<td>Difference from placebo (adjusted mean)</td>
<td>−0.7†</td>
</tr>
<tr>
<td></td>
<td>95% Confidence Interval</td>
<td>(−0.9, −0.5)</td>
</tr>
<tr>
<td>2-hour Postprandial Glucose (mg/dL)</td>
<td>N=115</td>
<td>N=113</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>268</td>
<td>262</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>−12</td>
<td>5</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean)</td>
<td>−17†</td>
<td>5‡</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(−32, −2)</td>
<td>(−22, −1)</td>
</tr>
</tbody>
</table>

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 or African American, 41.1% Asian, and 1.6% 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.

The majority of subjects were male (67%) and Caucasian (75%) with a mean age of 54.6 years, 1.6% were black or African American, 41.1% Asian, and 1.6% 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 10 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 to Dapagliflozin and Metformin

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

The known proportion of patients achieving HbA1c <7% at Week 24 was 35.3% in the saxagliptin treated group compared to 23.1% in the placebo treated group.

14.2 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=40) or severe (n=31) 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

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

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 ≥30 to ≤50 mL/min/1.73 m²) to severe (eGFR <30 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 53% 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 (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs] 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antiplatelet 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 ≥30 to ≤50 mL/min/1.73 m²) to severe (eGFR <30 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 53% 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 (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs] 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antiplatelet 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 SAVOR Study. Table 15: All-cause mortality by Treatment Group in the SAVOR Study

<table>
<thead>
<tr>
<th>Treatment 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>613 (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>Placebo</td>
<td>245 (3.0)</td>
<td>1.5</td>
<td>234 (2.8)</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>135 (1.6)</td>
<td>0.8</td>
<td>115 (1.4)</td>
<td>0.7</td>
<td></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

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

<table>
<thead>
<tr>
<th>Treatment 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>420 (5.1)</td>
<td>2.5</td>
<td>378 (4.6)</td>
<td>2.3</td>
<td>1.11 (0.96, 1.27)</td>
</tr>
<tr>
<td>Placebo</td>
<td>269 (3.2)</td>
<td>1.6</td>
<td>260 (3.2)</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>All-cause</td>
<td>151 (1.8)</td>
<td>0.9</td>
<td>118 (1.4)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CV death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ONGLYZA</td>
<td>16308.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>16156.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

17 PATIENT COUNSELING INFORMATION
Advising the patient to read 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 informed to contact their healthcare provider if they develop any unusual symptoms or if any existing symptoms persist 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)].

Heart Failure
Patients should be informed of the signs and symptoms of heart failure. Before initiating ONGLYZA, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Patients should be instructed to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [see Warnings and Precautions (5.2)].

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.

Severe and Disabling Arthralgia
Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs [see Warnings and Precautions (5.5)].

Bullous Pemphigoid
Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [see Warnings and Precautions (5.6)].

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.

ONGLYZA is a registered trademark of the AstraZeneca group of companies.

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AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
06/19 US-30447 6/19

Table 14: Major Adverse Cardiovascular Events (MACE) by Treatment Group in the SAVOR Study

<table>
<thead>
<tr>
<th>Event</th>
<th>ONGLYZA</th>
<th>Placebo</th>
<th>Hazard Ratio (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>690 (7.4)</td>
<td>3.8</td>
<td>609 (7.4)</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>115 (1.4)</td>
<td>0.7</td>
<td>118 (1.4)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Event</th>
<th>ONGLYZA</th>
<th>Placebo</th>
<th>Hazard Ratio (95.1% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>378 (4.6)</td>
<td>2.3</td>
<td>378 (4.6)</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>118 (1.4)</td>
<td>0.7</td>
<td>118 (1.4)</td>
</tr>
</tbody>
</table>

Table 16: ONGLYZA Tablet Presentations

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Film-Coated Tablet Color/Shape</th>
<th>Tablet Markings</th>
<th>Package Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>pink biconvex, round</td>
<td>“5” on one side and “4215” on the reverse, in blue ink</td>
<td>Bottles of 30</td>
<td>0310-6105-30 0310-6105-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bottles of 90</td>
<td></td>
</tr>
<tr>
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<td>Bottles of 30</td>
<td>0310-6100-30</td>
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<td>Bottles of 90</td>
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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)
- 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.

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.
- have or 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
  - 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.

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
  - skin rash, itching, flaking, or peeling
  - 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) 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
- 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.

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