

PRODUCT MONOGRAPH

 **ONGLYZA™**

saxagliptin tablets

(as saxagliptin hydrochloride)

5 mg

Oral Antihyperglycemic Agent

DPP-4 inhibitor

Incretin Enhancer

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Fr ONGLYZA™

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(as saxagliptin hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 5 mg	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

ONGLYZA (saxagliptin) is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a sulfonylurea, when metformin or the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control (see CLINICAL TRIALS).

Geriatrics (≥ 65 years of age): No dosage adjustment is required based on age, however greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (< 18 years of age): Safety and effectiveness of ONGLYZA in pediatric patients have not been established. Therefore, ONGLYZA should not be used in this patient population.

CONTRAINDICATIONS

Patients who have had a history of any serious hypersensitivity to this drug or to any ingredient in the formulation or to another DPP-4 inhibitor. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

ONGLYZA (saxagliptin) should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Endocrine and Metabolism

A lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions and DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. As animal reproduction studies are not always predictive of human response, ONGLYZA is not recommended for use in pregnancy (see TOXICOLOGY).

Nursing Women: Saxagliptin is secreted in the milk of lactating rats. It is not known whether saxagliptin is excreted in human milk. Therefore, ONGLYZA should not be used by a woman who is nursing.

Pediatrics (< 18 years of age): Safety and effectiveness of ONGLYZA in pediatric patients have not been established. Therefore, ONGLYZA should not be used in this patient population.

Geriatrics (≥ 65 years of age): Of the total number of subjects (N=4148) studied in controlled clinical safety and efficacy studies of ONGLYZA, 634 (15.3%) patients were 65 years and over, of which 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over 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 major metabolite are known to be eliminated in part by the kidney. Renal function should be assessed prior to initiating ONGLYZA and periodically thereafter in geriatric patients because they are more likely to have decreased renal function. Care should be taken in prescribing ONGLYZA in this population based on renal function (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Cardiovascular – Patients with Congestive Heart Failure: A limited number of patients with history of congestive heart failure participated in clinical studies with ONGLYZA. In clinical trials, ONGLYZA patients with NYHA Class III or IV congestive heart failure were excluded. Patients with history of congestive heart failure were included in small number (in total: 2% of patients exposed to ONGLYZA in clinical trials). Use in this population is not recommended.

Hepatic Insufficiency: There are limited clinical data in patients with hepatic impairment taking multiple doses of ONGLYZA. The use of ONGLYZA in patients with moderate to severe hepatic impairment is not recommended (see ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment: No dosage adjustment is recommended for patients with mild renal impairment.

Clinical experience with ONGLYZA in patients with moderate or severe renal insufficiency including those with end-stage renal disease (ESRD) requiring hemodialysis is limited. Use in these patients is not recommended. Assessment of renal function is recommended prior to initiation of ONGLYZA, and periodically thereafter (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Response should be monitored by periodic measurements of blood glucose and HbA1c levels. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

ONGLYZA (saxagliptin) was generally well tolerated in controlled clinical studies as an add-on to metformin and as an add-on to sulfonylurea with the overall incidence of adverse events similar to that reported with placebo.

In a placebo-controlled clinical study of patients receiving ONGLYZA 5 mg or placebo as an add-on to metformin, the incidence of serious adverse events was 9.9% and 5.6% respectively. The most commonly reported adverse events, reported regardless of causality and more common with ONGLYZA than placebo, were nasopharyngitis and bronchitis. Discontinuation of therapy due to adverse events occurred in 7.3% and 4.5% of patients, respectively.

In a placebo-controlled clinical study of patients receiving ONGLYZA 5 mg or placebo as an add-on to sulfonylurea (glyburide), the incidence of serious adverse events was 3.6% and 5.6% respectively. The most commonly reported adverse events, reported regardless of causality and more common with ONGLYZA than placebo, were hypoglycaemia and urinary tract infection. Discontinuation of therapy due to adverse events occurred in 4.7% and 3.4% of patients, respectively.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The incidence of adverse reactions, reported regardless of causality assessment, in $\geq 2\%$ of patients treated with either ONGLYZA 5 mg or placebo as an add-on to metformin or add-on to sulfonylurea (glyburide) are shown in Table 1.

Table 1 Adverse Reactions (Regardless of Investigator Assessment of Causality) in the Add-on to Metformin^a Study and in Add-on to Sulfonylurea^b Study (24-week Short Term Study and the Long Term Extension) Reported in $\geq 2\%$ of Patients Treated with Either ONGLYZA 5 mg or Placebo in at Least One Study

Body system/Organ Class Adverse Event	Number of Patients (%) Add-on to Metformin		Number of Patients (%) Add-on to Sulfonylurea	
	Saxagliptin 5 mg N=191	Placebo N=179	Saxagliptin 5 mg N=253	Placebo N= 267
Blood and lymphatic system disorders				
Anemia	11 (5.8)	3 (1.7)	2 (0.8)	3 (1.1)
Eosinophilia	6 (3.1)	0	1 (0.4)	1 (0.4)
Cardiac disorders				
Coronary artery disease	4 (2.1)	0	1 (0.4)	1 (0.4)
Gastrointestinal disorders				
Diarrhea	14 (7.3)	23 (12.8)	13 (5.1)	23 (8.6)
Dyspepsia	11 (5.8)	8 (4.5)	9 (3.6)	7 (2.6)
Toothache	8 (4.2)	11 (6.1)	8 (3.2)	8 (3.0)
Abdominal pain	7 (3.7)	2 (1.1)	6 (2.4)	4 (1.5)
Abdominal pain upper	7 (3.7)	5 (2.8)	10 (4.0)	8 (3.0)
Nausea	7 (3.7)	8 (4.5)	4 (1.6)	4 (1.5)
Vomiting	7 (3.7)	7 (3.9)	4 (1.6)	4 (1.5)
Constipation	5 (2.6)	3 (1.7)	2 (0.8)	3 (1.1)
Gastroesophageal reflux disease	4 (2.1)	1 (0.6)	2 (0.8)	6 (2.2)
Gastritis	2 (1.0)	2 (1.1)	5 (2.0)	8 (3.0)
General disorders and administration site conditions				
Edema peripheral	11 (5.8)	9 (5.0)	5 (2.0)	7 (2.6)
Chest pain	5 (2.6)	2 (1.1)	4 (1.6)	3 (1.1)
Fatigue	5 (2.6)	7 (3.9)	8 (3.2)	3 (1.1)
Asthenia	0	2 (1.1)	5 (2.0)	8 (3.0)
Infections and infestations				
Influenza	22 (11.5)	23 (12.8)	16 (6.3)	26 (9.7)
Nasopharyngitis	21 (11.0)	19 (10.6)	24 (9.5)	27 (10.1)
Bronchitis	18 (9.4)	11 (6.1)	8 (3.2)	7 (2.6)
Upper respiratory tract infection	17 (8.9)	14 (7.8)	22 (8.7)	22 (8.2)
Urinary tract infection	15 (7.9)	12 (6.7)	35 (13.8)	29 (10.9)
Sinusitis	10 (5.2)	9 (5.0)	4 (1.6)	3 (1.1)
Gastroenteritis	5 (2.6)	3 (1.7)	7 (2.8)	7 (2.6)
Tooth infection	5 (2.6)	3 (1.7)	2 (0.8)	2 (0.7)

Body system/Organ Class Adverse Event	Number of Patients (%) Add-on to Metformin		Number of Patients (%) Add-on to Sulfonylurea	
	Saxagliptin 5 mg N=191	Placebo N=179	Saxagliptin 5 mg N=253	Placebo N= 267
Gastroenteritis viral	4 (2.1)	2 (1.1)	1 (0.4)	1 (0.4)
Pharyngitis	2 (1.0)	4 (2.2)	19 (7.5)	14 (5.2)
Viral infection	1 (0.5)	4 (2.2)	4 (1.6)	6 (2.2)
Pharyngotonsillitis	1 (0.5)	1 (0.6)	5 (2.0)	10 (3.7)
Injury, poisoning, and procedural complications				
Limb Injury	3 (1.6)	1 (0.6)	0	7 (2.6)
Investigations				
Blood creatine phosphokinase increased	4 (2.1)	2 (1.1)	8 (3.2)	4 (1.5)
Alanine aminotransferase increased	1 (0.5)	4 (2.2)	4 (1.6)	3 (1.1)
Metabolism and nutrition disorders				
Hypoglycemia	17 (8.9)	18 (10.1)	50 (19.8)	49 (18.4)
Hypertriglyceridemia	6 (3.1)	2 (1.1)	9 (3.6)	5 (1.9)
Dyslipidemia	3 (1.6)	4 (2.2)	11 (4.3)	10 (3.7)
Musculoskeletal and connective tissue				
Arthralgia	16 (8.4)	9 (5.0)	17 (6.7)	20 (7.5)
Back pain	15 (7.9)	16 (8.9)	16 (6.3)	17 (6.4)
Osteoarthritis	8 (4.2)	4 (2.2)	2 (0.8)	7 (2.6)
Myalgia	6 (3.1)	4 (2.2)	6 (2.4)	5 (1.9)
Pain in extremity	6 (3.1)	13 (7.3)	12 (4.7)	18 (6.7)
Exostosis	4 (2.1)	2 (1.1)	1 (0.4)	1 (0.4)
Musculoskeletal pain	4 (2.1)	9 (5.0)	4 (1.6)	9 (3.4)
Muscle spasms	3 (1.6)	4 (2.2)	3 (1.2)	4 (1.5)
Nervous system disorders				
Headache	17 (8.9)	20 (11.2)	25 (9.9)	19 (7.1)
Dizziness	8 (4.2)	9 (5.0)	3 (1.2)	11 (4.1)
Parasthesia	0	2 (1.1)	1 (0.4)	6 (2.2)
Psychiatric disorders				
Anxiety	8 (4.2)	5 (2.8)	5 (2.0)	4 (1.5)
Depression	6 (3.1)	4 (2.2)	6 (2.4)	2 (0.7)
Renal and urinary disorders				
Microalbuminuria	5 (2.6)	4 (2.2)	3 (1.2)	2 (0.7)
Nephrolithiasis	4 (2.1)	3 (1.7)	0	4 (1.5)
Dysuria	0	4 (2.2)	5 (2.0)	7 (2.6)
Respiratory, thoracic, and mediastinal disorders				
Cough	7 (3.7)	9 (5.0)	14 (5.5)	16 (6.0)
Pharyngolaryngeal pain	5 (2.6)	3 (1.7)	3 (1.2)	4 (1.5)
Skin and subcutaneous tissue disorders				
Rash	6 (3.1)	5 (2.8)	1 (0.4)	2 (0.7)
Alopecia	4 (2.1)	0	0	1 (0.4)

Body system/Organ Class Adverse Event	Number of Patients (%) Add-on to Metformin		Number of Patients (%) Add-on to Sulfonylurea	
	Saxagliptin 5 mg N=191	Placebo N=179	Saxagliptin 5 mg N=253	Placebo N= 267
Pruritus	3 (1.6)	1 (0.6)	2 (0.8)	6 (2.2)
Vascular disorders				
Hypertension	9 (4.7)	12 (6.7)	21 (8.3)	13 (4.9)

^aThe mean duration of exposure to double-blind study medication, including exposure after the initiation of rescue medication, was 75 weeks (Standard Deviation = 34) for ONGLYZA 5 mg plus metformin and 68 weeks (Standard Deviation = 35) for placebo plus metformin groups.

^bThe mean duration of exposure to double-blind study medication, including exposure after the initiation of rescue medication, was 50 weeks (Standard Deviation = 17) for ONGLYZA 5 mg plus glyburide and 48 weeks (Standard Deviation = 17) for placebo plus uptitrated glyburide groups.

Rash-related adverse events in the add-on to metformin study (24-week short-term and long-term extension) were reported in 4.2% and 2.8% of patients who received ONGLYZA 5 mg and placebo, respectively. In the add-on to sulfonylurea study (24-week short-term and long-term extension) rash-related events were reported in 1.6 % and 1.1% of patients who received ONGLYZA 5 mg and placebo, respectively.

In a pooled analysis of the 24-week placebo-controlled clinical trials, hypersensitivity-related events, such as urticaria and facial edema were reported in 1.5% and 0.4% of patients who received 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.

In the short-term 24-week add-on to sulfonylurea study (glyburide 7.5 mg), the overall incidence of hypoglycemia was higher for ONGLYZA 5 mg versus placebo (14.6% versus 10.1%). The incidence of confirmed hypoglycemic events, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤ 2.8 mmol/L, was similar for ONGLYZA 5 mg treated group (0.8%) and placebo group (0.7%). In the long-term extension of the add-on to sulfonylurea study, the overall incidence of hypoglycemia was similar for ONGLYZA 5 mg (19.8%) versus uptitrated sulfonylurea plus placebo (19.8% versus 18.4%).

The adverse event of hypertension was reported in more patients on ONGLYZA 5 mg plus glyburide (8.3%) versus placebo plus glyburide (4.9%) in the add-on to sulfonylurea trial. Analysis of the mean systolic and diastolic blood pressure values did not reveal clinically meaningful changes.

Serious Adverse Reactions (reported in < 2% of patients) and Adverse Reactions of Interest* (reported in < 2% of patients and in at least 2 patients), Regardless of Investigator Assessment of Causality and Frequency > Placebo, in the Add-on to Metformin and Add-on to Sulfonylurea Studies (24-week short-term and the long-term extensions)

* System Organ Classes were considered to be of interest based on the adverse event profile of the DPP-4 inhibitor class of drugs, non-clinical data for saxagliptin, as well as the patient population.

Blood and lymphatic system disorders*: eosinophilia, lymphopenia, iron deficiency anemia, normochromic normocytic anemia

Cardiac disorders*: coronary artery disease, left ventricular hypertrophy, atrioventricular block first degree, bundle branch block left, mitral valve incompetence, myocardial ischemia, palpitations, ventricular extrasystoles, acute myocardial infarction, atrioventricular block complete, cardiac failure congestive, cardiogenic shock

Gastrointestinal disorders: abdominal pain, diarrhea, salivary gland mass, vomiting

Hepatobiliary disorders: cholecystitis acute, cholecystitis

Immune system disorders*: hypersensitivity, sarcoidosis

Infections and infestations: cellulitis orbital, clostridium difficile colitis, urosepsis, diverticulitis

Injury, poisoning and procedural complications: road traffic accident, ankle fracture, fall, gastrointestinal injury, incisional hernia, limb injury, skin laceration

Investigations*: aspartate aminotransferase increased, c-reactive protein increased, electrocardiogram repolarisation abnormality, blood cholesterol increased, blood pressure increased, electrocardiogram abnormal, lymphocyte count decreased

Metabolism and nutrition disorders: dehydration

Musculoskeletal and connective tissue disorders: arthralgia, osteoarthritis

Neoplasms benign, malignant and unspecified (including cysts and polyps): myelodysplastic syndrome

Nervous system disorders: altered state of consciousness, dizziness

Renal and urinary disorders: calculus ureteric, calculus urinary

Respiratory, thoracic and mediastinal disorders: hemoptysis, pulmonary embolism

Skin and subcutaneous tissue disorders*: rash, alopecia, dermatitis atopic, hyperhidrosis, rash papular, skin lesion, dermatitis contact, dermatitis, dry skin, seborrhoeic dermatitis, urticaria

Surgical and medical procedures: sterilisation

Abnormal Hematologic and Clinical Chemistry Findings

Absolute Lymphocyte Counts: A dose-related mean decrease in absolute lymphocyte count was observed with ONGLYZA. From a baseline absolute lymphocyte count of approximately 2200 cells/ μ L, a mean decrease of approximately 100 cells/ μ L relative to placebo was observed in a pooled analysis of the placebo-controlled clinical studies. The proportion of patients who were reported to have a lymphocyte count \leq 750 cells/ μ L was 1.5% in the ONGLYZA 5 mg group and 0.4% in the placebo group. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. When clinically indicated, such

as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g. human immunodeficiency virus) is unknown.

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

DRUG INTERACTIONS

The metabolism of saxagliptin is primarily mediated by P450 3A4/5 (CYP3A4/5).

In *in vitro* studies, saxagliptin and its major pharmacologically active metabolite neither inhibited nor induced CYP3A4. In addition, in *in vitro* studies, saxagliptin and its major pharmacologically active metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, nor induced CYP1A2, 2B6, 2C9. Therefore, saxagliptin is unlikely to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is neither a significant inhibitor of P-glycoprotein (P-gp) nor an inducer of P-gp, and is unlikely to cause interactions with drugs that utilize these pathways.

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

Drug-Drug Interactions

Effect of other drugs on saxagliptin

In studies conducted in healthy subjects as described below, the pharmacokinetics of saxagliptin and its major metabolite were not meaningfully altered by metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, omeprazole, aluminum hydroxide + magnesium hydroxide + simethicone combination, or famotidine. These drugs are considered unlikely to cause a clinically meaningful interaction with ONGLYZA.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an OCT-1 and OCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged. Therefore, metformin is considered unlikely to cause a clinically meaningful interaction with ONGLYZA. Meaningful interactions of ONGLYZA with other OCT-1 and OCT-2 substrates would not be expected.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, did not affect the pharmacokinetics of saxagliptin. Therefore, glyburide is considered unlikely to cause a clinically meaningful interaction with ONGLYZA. Meaningful interactions of ONGLYZA with other CYP2C9 substrates would not be expected.

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

pharmacokinetics of saxagliptin. Therefore, pioglitazone is considered unlikely to cause a clinically meaningful interaction with ONGLYZA. Meaningful interactions of ONGLYZA with other CYP2C8 substrates would not be expected.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin. Therefore, digoxin is considered unlikely to cause a clinically meaningful interaction with ONGLYZA. Meaningful interactions of ONGLYZA with other P-gp substrates would not be expected.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged. Therefore, simvastatin is considered unlikely to cause a clinically meaningful interaction with ONGLYZA. Meaningful interactions of ONGLYZA would not be expected with other substrates of CYP3A4/5.

Diltiazem: Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} and AUC for saxagliptin by 63% and 109%, respectively. This coadministration was also associated with 44% and 34% decreases in C_{max} and AUC(INF) values, respectively of its major metabolite. Therefore, diltiazem is considered unlikely to cause a clinically meaningful interaction with ONGLYZA. Meaningful interactions of ONGLYZA with other moderate CYP3A4/5 inhibitors would not be expected.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, increased the C_{max} and AUC for saxagliptin by 62% and 145 % respectively. This coadministration was also associated with 95% and 88% decreases in C_{max} and AUC(INF) values, respectively of its major metabolite.

Following co-administration of a single dose of saxagliptin at 20 times the recommended dose (100 mg) with ketoconazole, transient flu-like symptoms and a transient decrease in absolute lymphocyte count were observed. Additionally, transient decreases in absolute lymphocyte count were observed without any flu-like symptoms following co-administration of a single dose of saxagliptin at 4 times the recommended dose (20 mg) with ketoconazole.

CYP3A4/5 Inducers: The effects of CYP3A4/5 inducers on the pharmacokinetics of saxagliptin have not been studied. However, the coadministration of saxagliptin and CYP3A4/5 inducers such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampin may result in decreased plasma concentrations of saxagliptin and increased concentrations of its major metabolite.

Omeprazole: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin. Therefore, omeprazole is considered unlikely to cause a clinically meaningful interaction with

ONGLYZA. Meaningful interactions of ONGLYZA with other CYP2C19 inhibitors or MRP-3 inducers would not be expected.

Aluminum hydroxide + magnesium hydroxide + simethicone: Coadministration of a single dose of saxagliptin (10 mg) and a liquid containing aluminum hydroxide (2400 mg), magnesium hydroxide (2400 mg), and simethicone (240 mg) decreased the C_{max} of saxagliptin by 26%; however, the AUC of saxagliptin was unchanged. Therefore, meaningful interactions of ONGLYZA with antacid and antigas formulations of this type would not be expected.

Famotidine: Administration of a single dose of saxagliptin (10 mg) three hours after a single dose of famotidine (40 mg), an inhibitor of hOCT-1, hOCT-2, and hOCT-3, increased the C_{max} of saxagliptin by 14%; however, the AUC of saxagliptin was unchanged. Therefore, famotidine is considered unlikely to cause a clinically meaningful interaction with ONGLYZA. Meaningful interactions of ONGLYZA would not be expected with other inhibitors of hOCT-1, hOCT-2, and hOCT-3.

Effect of saxagliptin on other drugs

In studies conducted in healthy subjects, as described below, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole. ONGLYZA is considered unlikely to cause a clinically meaningful interaction with these drugs.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an OCT-1 and OCT-2 substrate, did not alter the pharmacokinetics of metformin in healthy subjects. Therefore, ONGLYZA is considered unlikely to cause a clinically meaningful interaction with metformin. ONGLYZA is not an inhibitor of OCT-1 and OCT-2-mediated transport.

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

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 substrate, increased the plasma C_{max} of pioglitazone by 14%; however, the AUC of pioglitazone was unchanged. Therefore, ONGLYZA is considered unlikely to cause a clinically meaningful interaction with pioglitazone. ONGLYZA does not meaningfully inhibit or induce CYP2C8-mediated metabolism.

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

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

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

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and multiple doses of ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, decreased the geometric means for C_{max} and AUC(INF) of ketoconazole by 16 % and by 13% respectively, relative to those observed following administration of 200 mg ketoconazole q 12 h alone.

Drug-Food Interactions

There are no known interactions with food. Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism may give rise to modest increases in plasma levels of saxagliptin.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No studies of the effects of ONGLYZA on the ability to drive and use machines have been performed. However, ONGLYZA is not expected to affect the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ONGLYZA (saxagliptin) may be taken with or without food.

Recommended Dose and Dosage Adjustment

The recommended dose of ONGLYZA is 5 mg once daily.

Renal Impairment: Use of ONGLYZA in patients with moderate to severe renal impairment, including patients with end stage renal disease requiring hemodialysis is not recommended.

Hepatic Impairment: Use of ONGLYZA in patients with moderate to severe hepatic impairment is not recommended due to lack of clinical experience with this patient population.

Pediatrics (<18 years of age): Safety and effectiveness of ONGLYZA in pediatric patients have not been established. Therefore, ONGLYZA should not be used in this patient population.

Geriatrics (≥65 years of age): No dosage adjustment for ONGLYZA is required based solely on age (see WARNINGS AND PRECAUTIONS, CLINICAL TRIALS and ACTION AND CLINICAL PHARMACOLOGY).

Missed Dose

If a dose of ONGLYZA is missed, it should be taken as soon as the patient remembers. A double dose of ONGLYZA should not be taken on the same day.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Saxagliptin is a potent, selective, reversible, competitive, DPP-4 inhibitor. Saxagliptin demonstrates selectivity for DPP-4 versus other DPP enzymes, including DPP-8 and DPP-9. Saxagliptin has extended binding to the DPP-4 active site, prolonging its inhibition of DPP-4⁵. Saxagliptin exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1). The concentration of active (intact) GLP-1 incretin hormone is increased.

Incretin hormones are released by the intestine throughout the day and concentrations are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

The concentration of GLP-1 is reduced in patients with type 2 diabetes⁷, but saxagliptin increases active GLP-1 concentration. By increasing active GLP-1 concentration, saxagliptin increases postprandial insulin release and decreases postprandial glucagon concentrations in the circulation in a glucose-dependent manner. In patients with type 2 diabetes with

hyperglycemia, these changes in insulin and glucagon levels may lead to lower hemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations.³

Pharmacodynamics

In patients with type 2 diabetes, administration of ONGLYZA (saxagliptin) led to dose-dependent inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1, decreased postprandial glucagon concentrations, and increased glucose-dependent beta cell responsiveness with higher postprandial insulin and C-peptide concentrations. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac electrophysiology: In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study, 40 healthy subjects were administered saxagliptin 40 mg (8 times the RHD), saxagliptin 10 mg (2 times the RHD), or placebo once daily for 4 days, or a single dose of moxifloxacin 400 mg as a positive control. The saxagliptin 10 mg and 40 mg treatments were not associated with any prolongation of the QTc, QRS, or PR intervals. In the saxagliptin 10 mg treatment a significant increase in heart rate was observed at 0.5, 1, 1.5, 4, and 12 h post-dosing, with a maximum placebo- and baseline-corrected mean increase of 3.75 (90% 1.55, 5.95) beats per minute at 0.5 post-dosing when the baseline-corrected change in the placebo treatment at this time was -1.4 (90% CI -3.0, 0.1) beats per minute. Significant increases in heart rate were also observed in the saxagliptin 40 mg treatment at 0.5, 4, and 12 hours post-dosing, with a maximum placebo- and baseline-corrected mean increase of 4.5 (90% CI 2.23, 6.82) beats per minute at 4 hours post-dose dose when the baseline-corrected change in the placebo treatment at this time was -3.3 (90% CI -5.0, -1.6) beats per minute. The effect of the recommended 5 mg dose was not investigated in this study.

Pharmacokinetics

The pharmacokinetics of saxagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes (Table 2).

Table 2 Summary of saxagliptin's pharmacokinetic parameters in healthy subjects

	C_{max} (ng/mL)	t_{1/2} (h)	AUC ng·h/mL	Renal Clearance (mL/min)
Single oral dose (5 mg) mean	24	2.5	78	230

Saxagliptin was rapidly absorbed after oral administration, with maximum saxagliptin plasma concentrations (C_{max}) usually attained within two hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in the saxagliptin dose. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC(INF) values for saxagliptin and its major metabolite were 78 ng·h/mL and 214 ng·h/mL,

respectively. The corresponding plasma C_{\max} values were 24 ng/mL and 47 ng/mL, respectively. The intra-subject coefficients of variation for saxagliptin C_{\max} and AUC were less than 12%.

Following a single oral dose of 5 mg saxagliptin to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin was 2.5 hours, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. The inhibition of plasma DPP-4 activity by saxagliptin occurs for at least 24-hours after oral administration of ONGLYZA. No appreciable accumulation was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg. Results from population-based exposure modeling suggest that the pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption: ONGLYZA may be administered with or without food. The amount of saxagliptin absorbed following an oral dose is at least 75%. Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with a high-fat meal resulted in no change in saxagliptin C_{\max} and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach C_{\max} (T_{\max}) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Distribution: The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Thus, 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 selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

Excretion: Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C -saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major 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. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. 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.

Pharmacokinetics of the Major Metabolite: The C_{\max} and AUC values for the major metabolite of saxagliptin increased proportionally to the increment in the saxagliptin dose. Following single oral doses of 2.5 mg to 400 mg saxagliptin in the fed or fasted states, the mean AUC values for the major metabolite ranged from 2- and 7 times higher than the parent saxagliptin exposures on a molar basis. Following a single oral dose of 10 mg saxagliptin in

the fasted state, the mean terminal half-life ($t_{1/2}$) value for the major metabolite was 3.1 hours and no appreciable accumulation was observed upon repeated once-daily dosing at any dose.

Special Populations and Conditions

Pediatrics (< 18 years of age): Pharmacokinetics in the pediatric population have not been studied. Therefore, ONGLYZA should not be used in this patient population.

Geriatrics (\geq 65 years of age): No dosage adjustment is necessary based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for parent saxagliptin than young subjects (18-40 years). Differences in major metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in parent saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the major metabolite in young and elderly subjects is likely to be due to multiple factors including declining renal function and metabolic capacity with increasing age.

Gender: No dosage adjustment is necessary based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the major metabolite than males, but the clinical relevance of this difference is unknown.

Race: No dosage adjustment is necessary based on race. An exposure modeling analysis compared the pharmacokinetics of saxagliptin and its major metabolite in 309 white subjects with 105 non-white subjects (consisting of 6 race groups). No significant difference in the pharmacokinetics of saxagliptin and its major metabolite were detected between these two populations.

Body Mass Index: No dosage adjustment is recommended based on body mass index (BMI).

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

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

In subjects with mild renal impairment, the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended.

In subjects with moderate or severe renal impairment or in subjects with ESRD on hemodialysis, the AUC values of saxagliptin and its major metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. Therefore use in this population is not recommended.

Hepatic Impairment: In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the major metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. Use in moderate to severe hepatic impairment is not recommended.

STORAGE AND STABILITY

Temperature: Store at room temperature (15-30°C).

Others: Keep in a safe place out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

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.

The 5 mg tablets are provided in blisters in cartons of 30 or 100.

Information for the patient is provided as a package insert in the ONGLYZA packages.

Composition

ONGLYZA tablets contain the following non-medicinal 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. The printing ink contains FD&C Blue #2 and shellac glaze.

PART II: SCIENTIFIC INFORMATION

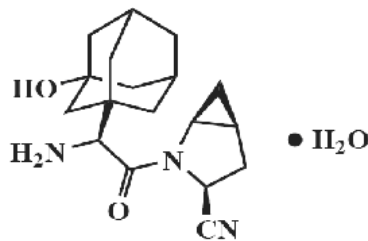
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	saxagliptin monohydrate ^a
Chemical Name:	2-azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2 <i>S</i>)-2-amino-2-(3-hydroxytricyclo[3.3.1.1 ^{3,7}]dec-1-yl)acetyl]-, hydrate (1:1), (1 <i>S</i> ,3 <i>S</i> ,5 <i>S</i>)- or (1 <i>S</i> ,3 <i>S</i> ,5 <i>S</i>)-2-[(2 <i>S</i>)-amino(3-hydroxytricyclo[3.3.1.1 ^{3,7}]dec-1-yl)acetyl]2-azabicyclo[3.1.0]hexane-3-carbonitrile monohydrate

Molecular Formula and Molecular Mass: C₁₈H₂₅N₃O₂·H₂O
333.43; (315.41 anhydrous)

Structural Formula:



Physicochemical Properties:

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

^asaxagliptin monohydrate is converted to saxagliptin hydrochloride *in-situ* during drug product manufacturing

CLINICAL TRIALS

Study demographics and trial design

Table 3 Summary of patient demographics for clinical trials in specific indication

Trial design	Dosage, route of administration and duration	Study subjects per treatment arm Subjects ≥ 65 years of age Subjects ≥ 75 years of age (N=number)	Mean age (Range)	Gender (% M/F)
Add-on Combination Therapy with Metformin				
Multicentre, randomized, double-blind, placebo-controlled	open-label metformin (1500 – 2500 mg) plus saxagliptin 5 mg or placebo Oral, 24 weeks	Saxagliptin 5 mg N=191 ≥ 65 years N=32 ≥ 75 years N=2 Placebo N= 179 ≥ 65 years n=26 ≥ 75 years n=3	55 years (26 - 76)	54/46
Add-on Combination Therapy with a Sulfonylurea				
Multicentre, randomized, double-blind, placebo-controlled	open-label glyburide 7.5 mg plus saxagliptin 5 mg or open-label glyburide 7.5 mg plus double-blind glyburide 2.5 mg (total daily dose of 10 mg titratable to 15 mg) plus placebo Oral, 24 weeks	Saxagliptin 5 mg N=253 ≥ 65 years N=42 ≥ 75 years N=3 Placebo N=267 ≥ 65 years n=52 ≥ 75 years n=5	55 years (18 - 77)	45/55

Study results

In patients with type 2 diabetes, the treatment with ONGLYZA (saxagliptin) 5 mg produced clinically relevant and statistically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and postprandial glucose (PPG), including 2-hour PPG following standard oral glucose tolerance test (OGTT), compared to control.

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control

(A1C \geq 7% and \leq 10%) on metformin alone. Patients were required to be on a stable dose of metformin (1500 mg to 2550 mg daily) for at least 8 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, two-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to placebo or ONGLYZA plus metformin. Dose titrations of ONGLYZA and metformin were not allowed in this study.

In combination with metformin, ONGLYZA 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus metformin group (Table 4).

Table 4 Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA in Combination with Metformin[§]

Efficacy Parameter	ONGLYZA 5 mg + Metformin	Placebo + Metformin
A1C (%)	N=186	N=175
Baseline (mean)	8.1	8.1
Change from baseline (adjusted mean [±])	-0.7	0.1
Difference from placebo (adjusted mean [±])	-0.8 ^a	
95% Confidence Interval	(-1.0, -0.6)	
Percent of patients achieving A1C <7%	44% ^a (81/186)	17% (29/175)
FPG (mmol/L)	N=187	N=176
Baseline (mean)	9.9	9.7
Change from baseline (adjusted mean [±])	-1.2	0.07
Difference from placebo (adjusted mean [±])	-1.3 ^a	
95% Confidence Interval	(-1.7, -0.9)	
2-hour PPG (mmol/L)	N=155	N=135
Baseline (mean)	16.4	16.4
Change from baseline (adjusted mean [±])	-3.2	-1.0
Difference from placebo (adjusted mean [±])	-2.2 ^a	
95% Confidence Interval	(-3.1, -1.3)	
3-hour PPG AUC (mmol*min/L)	N=146	N=131
Baseline (mean)	2721	2631
Change from baseline (adjusted mean [±])	-532	-183
Difference from placebo (adjusted mean [±])	-349 ^a	
95% Confidence Interval	(-478, -221)	

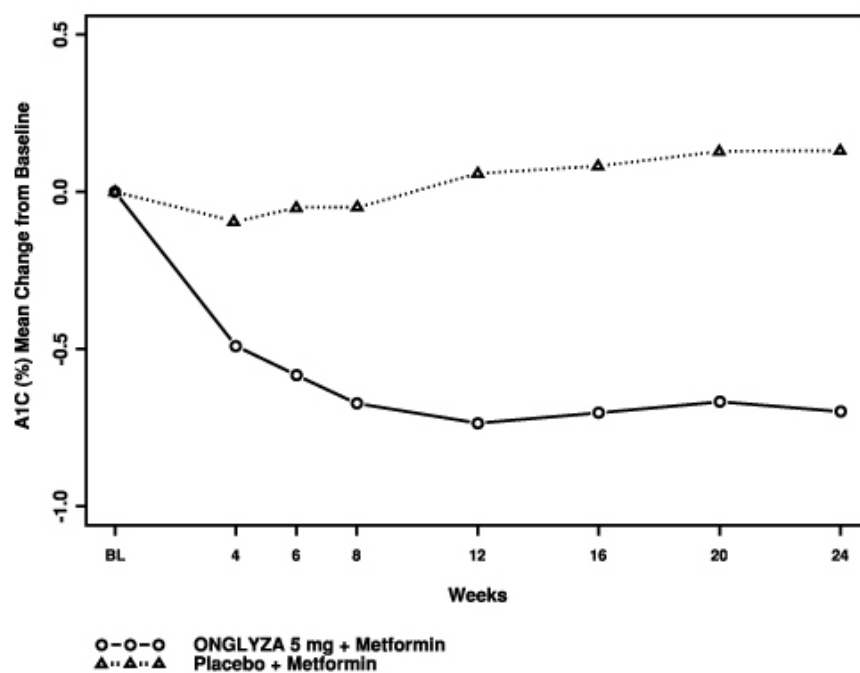
§ Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.

± Least squares mean adjusted for baseline value.

a p-value <0.0001 compared to placebo

The mean percent change from baseline in A1C over the 24-week period is shown in Figure 1. The proportion of patients achieving A1C <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus metformin treatment (43.5%) groups compared with the placebo plus metformin group (16.6%). Significant reductions in 2-hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus metformin treatment group (-3.2 mmol/L) compared with -1.0 mmol/L in the placebo plus metformin group. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was higher in the placebo plus metformin group (27%) than in the ONGLYZA 5 mg plus metformin group (13%). Higher baseline A1C was associated with a greater adjusted mean change from baseline in A1C with ONGLYZA 5 mg. The effect of ONGLYZA on lipid endpoints in this study was similar to placebo. Similar changes in body weight were observed in patients who received ONGLYZA and placebo therapy (-0.9 kg and -0.9 kg, respectively).

Figure 1 Mean Change from Baseline in A1C in a Placebo-Controlled Study of ONGLYZA in Combination with Metformin*



*Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Patients who completed all visits during the initial 24-week study period without need for hyperglycemia rescue therapy were eligible to enter a controlled double blind long-term study extension. Of the patients that started the 24-week treatment, 162 (84.8%) and 149 (83.2%) patients were taking ONGLYZA 5 mg plus metformin and placebo plus metformin respectively. Patients who received ONGLYZA in the initial 24-week study period

maintained the same dose of ONGLYZA in the long-term extension. Treatment with ONGLYZA 5 mg plus metformin was associated with a greater reduction in A1C than in the placebo plus metformin group, and the effect relative to placebo was sustained at Week 50 and Week 102 compared to placebo. The A1C change for ONGLYZA 5 mg plus metformin (n=100 observed, n=187 LOCF) compared with placebo plus metformin (n=59 observed, n=175 LOCF) was -0.7% at Week 50. The A1C change for ONGLYZA 5 mg plus metformin (n=31 observed, n=184 LOCF) compared with placebo plus metformin (n=15 observed, n=172 LOCF) was -0.7% at Week 102.

Add-On Combination Therapy with a Sulfonylurea

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

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period and placed on glyburide 7.5 mg once daily. Following the lead-in period, eligible patients with A1C $\geq 7\%$ to $\leq 10\%$ were randomized to either 2.5 mg or 5 mg of ONGLYZA plus 7.5 mg glyburide, or 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 allowed in patients who received ONGLYZA 2.5 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 study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to the ONGLYZA plus glyburide or the placebo plus up-titrated glyburide group. Dose titration of ONGLYZA was not permitted during the study.

In combination with glyburide, ONGLYZA 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus up-titrated glyburide group (Table 5). The mean percent change from baseline in A1C over the 24-week period is shown in Figure 2. The proportion of patients achieving A1C $<7.0\%$ (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus glyburide treatment group (22.8%) compared with the placebo plus up-titrated glyburide group (9.1%). Significant reductions in 2 hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus glyburide treatment group (-1.9 mmol/L) compared with 0.4 mmol/L in the placebo plus up-titrated glyburide group. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was higher in the placebo plus up-titrated glyburide group (30%) than in the ONGLYZA 5 mg plus glyburide group (17%). Higher baseline A1C was associated with a greater adjusted mean change from baseline in A1C with ONGLYZA 5 mg. The effect of ONGLYZA on lipid endpoints in this

study was similar to placebo. Small increases in body weight were seen in patients treated with ONGLYZA 5 mg plus glyburide and with placebo plus up-titrated glyburide (0.8 kg versus 0.3 kg, p=0.012).

Table 5 Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA in Combination with Glyburide[§]

Efficacy Parameter	ONGLYZA 5 mg + Glyburide 7.5 mg	Placebo + Up-Titrated Glyburide
A1C (%)	N=250	N=264
Baseline (mean)	8.5	8.4
Change from baseline (adjusted mean [±])	-0.6	0.1
Difference from up-titrated glyburide (adjusted mean [±])	-0.7 ^a	
95% Confidence Interval	(-0.9, -0.6)	
Percent of patients achieving A1C <7%	23% ^a (57/250)	9% (24/264)
FPG (mmol/L)	N=252	N=265
Baseline (mean)	9.7	9.7
Change from baseline (adjusted mean [±])	-0.5	0.04
Difference from up-titrated glyburide (adjusted mean [±])	-0.6 ^b	
95% Confidence Interval	(-0.9, -0.2)	
2-hour PPG (mmol/L)	N=202	N=206
Baseline (mean)	17.5	17.9
Change from baseline (adjusted mean [±])	-1.9	0.4
Difference from placebo (adjusted mean [±])	-2.3 ^a	
95% Confidence Interval	(-2.9, -1.7)	
3-hour PPG AUC (mmol*min/L)	N=195	N=204
Baseline (mean)	2794	2875
Change from baseline (adjusted mean [±])	-278	66
Difference from up-titrated glyburide (adjusted mean [±])	-344 ^a	
95% Confidence Interval	(-433, -254)	

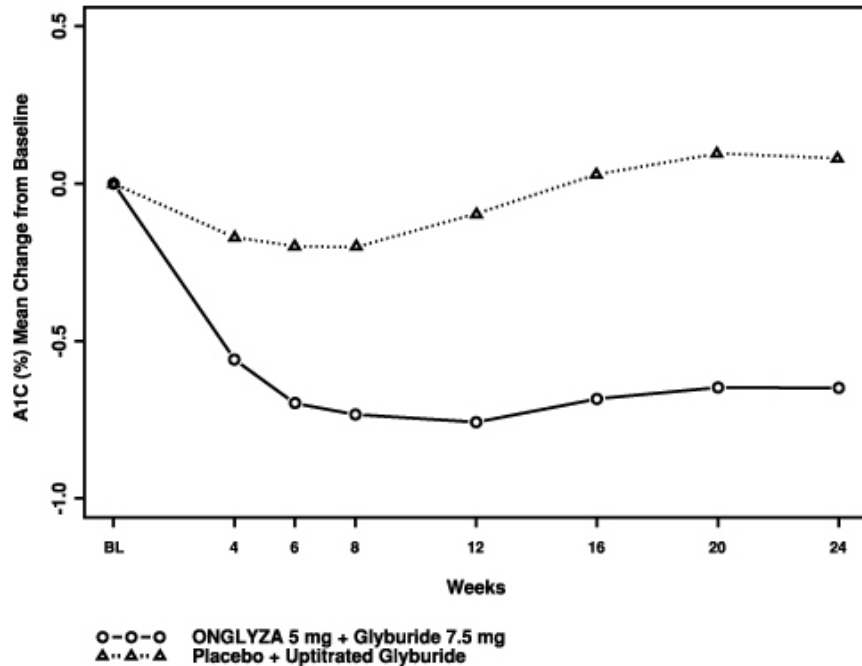
§ Intent-to-treat population using last observation on study prior to metformin rescue therapy.

± Least squares mean adjusted for baseline value.

a p-value <0.0001 compared to placebo + up-titrated glyburide

b p-value=0.0020 compared to placebo + up-titrated glyburide

Figure 2 Mean Change from Baseline in A1C in a Placebo-Controlled Study of ONGLYZA in Combination with Glyburide*



* Intent-to-treat population using last observation on study prior to metformin rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Patients who completed all visits during the 24-week study period without need for hyperglycemia rescue therapy were eligible to enter a controlled double blind long-term study extension. Of the patients that started the 24-week treatment, 227 (89.7%) and 235 (88%) patients were taking ONGLYZA 5 mg plus glyburide and placebo plus up-titrated glyburide respectively. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. The A1C change for ONGLYZA 5 mg plus glyburide (n=99 observed, n=243 LOCF) compared with placebo plus up-titrated glyburide (n=61 observed, n=253 LOCF) was -0.6% at Week 50.

DETAILED PHARMACOLOGY

Saxagliptin and its major metabolite are potent reversible inhibitors of DPP-4 *in vitro* with selectivity for DPP-4 versus other enzymes, including other DPP family members such as DPP-8 and DPP-9. Saxagliptin and its major metabolite have extended binding to the DPP-4 active site, prolonging their activity, but do not have extended duration of binding to other enzymes, including DPP-8 and DPP-9. Saxagliptin was a potent inhibitor of T-cell cell surface DPP activity in cell based assays, but did not inhibit T-cell activation either *in vitro* or *in vivo*.

Saxagliptin, when dosed orally, demonstrated dose-related inhibition of DPP-4 in *ex vivo* assays in rats, dogs and cynomolgus monkeys. In acute *in vivo* studies, saxagliptin increased concentrations of intact GLP-1 in response to a meal in lean rats (maximum effect at 1 mg/kg). Saxagliptin also increased plasma insulin and lowered plasma glucose following an oral glucose tolerance test in obese insulin resistant and diabetic animal rodent models (maximum effect range 0.4 to 1.3 mg/kg). In chronic dosing studies using the progressively diabetic ZDF rat model, saxagliptin (4 mg/kg/day) delayed development of fasting hyperglycemia and the results of oral glucose tolerance tests showed significantly improved glucose homeostasis. These results are consistent with the mechanism of action of saxagliptin and its effects as an anti-hyperglycemic agent.

TOXICOLOGY

Acute Toxicity

Saxagliptin was observed to be well tolerated at single doses up to 2000 mg/kg in mice and rats and 25 mg/kg in cynomolgus monkeys. In rodents, 4000 mg/kg resulted in transient decreases in body-weight gain and activity and/or lethality. In monkeys, overt toxicity and lethality were observed at 50 mg/kg.

Chronic Toxicity

The potential toxicity of saxagliptin was evaluated in a number of repeat-dose studies in mice, rats, dogs and monkeys. Saxagliptin administered to rats for 6 months at doses of 2, 20 and 100 mg/kg/day was well tolerated, causing only at the high dose, minimal splenic lymphoid hyperplasia and pulmonary histiocytosis. The no-observed-adverse-effect-level (20 mg/kg/day) was 36 times (males) and 78 times (females) the human exposure based on the recommended human dose of 5 mg/day (RHD). In dogs, saxagliptin administered orally at 5 and 10 mg/kg/day for 12 months caused toxicity in the intestinal tract, as evidenced by bloody and mucoid feces. The no-observed-adverse-effect-level was 1 mg/kg/day, 4 times the RHD. In monkeys, major target organ changes included skin lesions (scabs, erosions, and ulceration), lymphoid hyperplasia (primarily spleen and bone marrow) and multi-tissue mononuclear-cell infiltrates. Skin healing during the dosing period was observed with recovery of both skin and microscopic changes following a drug-free recovery period. The AUCs at the no effect level for these changes were 1 to 3 times the RHD.

Carcinogenicity

Two-year carcinogenicity studies were conducted in mice and rats at oral doses of 50, 250, and 600 mg/kg/day and 25, 75, 150, and 300 mg/kg/day, respectively. Saxagliptin did not induce tumors in either mice or rats at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 900 (males) and 1210 (females) times the human exposure at the recommended human dose of 5 mg/day (RHD). In rats, AUC exposures were approximately 370 (males) and 2300 (females) times the RHD.

Mutagenesis

The mutagenic and clastogenic potential of saxagliptin was tested at high concentrations and exposures in a battery of genetic toxicity studies including an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. Saxagliptin was not mutagenic or clastogenic based on the combined outcomes of these studies. The major metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

Reproduction

In a rat fertility study, males were treated with oral gavage doses of 100, 200, and 400 mg/kg/day for two weeks prior to mating, during mating, and up to scheduled termination (approximately four-weeks total) and females were treated with oral gavage doses of 125, 300, and 750 mg/kg/day for two weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at 200 mg/kg/day (males) or 125 mg/kg/day (females) resulting in respective exposures (AUC) of approximately 630 (males) and 805 (females) times human exposure at the RHD. At higher, maternally toxic doses (300 and 750 mg/kg/day), increased fetal resorptions were observed (approximately 2150 and 6375 times the RHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at 750 mg/kg (approximately 6375 times the RHD).

Development

Saxagliptin was not teratogenic at any dose evaluated in rats or rabbits. At high doses in rats, saxagliptin caused a minor and reversible developmental delay in ossification of the fetal pelvis at ≥ 240 mg/kg/day (≥ 1560 times the human exposure [AUC] at the RHD). Maternal toxicity and reduced fetal body weights were observed at 900 mg/kg/day (8290 times the RHD). In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (200 mg/kg/day, exposures 1420 times the RHD).

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (≥ 250 mg/kg/day, exposures ≥ 1690 times the RHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

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PART III: CONSUMER INFORMATION

Pr ONGLYZA™
saxagliptin tablets
(as saxagliptin hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when ONGLYZA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ONGLYZA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

WHAT THE MEDICATION IS USED FOR:

ONGLYZA is used to improve blood sugar levels in adult patients with type 2 diabetes, in combination with metformin or sulfonylurea when diet and exercise and metformin or sulfonylurea alone have failed to adequately control blood sugar levels.

WHAT IT DOES:

ONGLYZA belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). ONGLYZA helps to improve blood sugar levels in response to a meal. ONGLYZA also lowers blood sugar levels between meals, and helps to decrease the amount of sugar made by your body.

What is Type 2 Diabetes?

Insulin is a hormone that helps control the level of sugar (glucose) in your blood. Type 2 diabetes is a condition in which your body does not make enough insulin and/or the insulin that your body produces does not work as well as it should. When this happens, glucose can build up in the blood. This can lead to serious problems.

WHEN IT SHOULD NOT BE USED:

Do not take ONGLYZA if you are allergic to any of the ingredients in ONGLYZA or if you are allergic to the other drugs belonging to DPP-4 class.

WHAT THE MEDICINAL INGREDIENT IS:

ONGLYZA contains saxagliptin (as saxagliptin hydrochloride) the active ingredient.

WHAT THE IMPORTANT NONMEDICINAL INGREDIENTS ARE:

ONGLYZA tablets contain the following non-medicinal 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. The printing ink contains FD&C Blue #2 and shellac glaze.

WHAT DOSAGE FORMS IT COMES IN:

ONGLYZA is supplied in 5 mg saxagliptin (as saxagliptin hydrochloride) tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use ONGLYZA talk to your doctor or pharmacist if:

- you have type 1 diabetes
- you have or have had diabetic ketoacidosis (increased ketones in the blood or urine)
- you have had an allergic reaction to ONGLYZA or other DPP-4 inhibitors
- you have or have had any kidney problems
- you have or have had liver problems
- you have heart failure
- you are pregnant or planning to become pregnant
- you are breast-feeding or plan to breast-feed

INTERACTIONS WITH THIS MEDICATION

Talk to your doctor or pharmacist about all the drugs you take. This includes prescription drugs, as well as those you buy yourself, and herbal supplements.

PROPER USE OF THIS MEDICATION

Follow the directions given to you by your doctor.

USUAL DOSE:

The recommended adult dose is 5 mg, once daily, taken with or without food.

OVERDOSE:

If you think you have taken too much ONGLYZA, call your doctor or pharmacist right away, or contact your local poison control centre immediately.

MISSED DOSE:

If you miss a dose of ONGLYZA, take it as soon as you remember. If you do not remember until it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The common side effects of ONGLYZA include: upper respiratory tract infection, urinary tract infection and headache. Hypoglycemia may occur more frequently in people who already take a sulfonylurea. 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, and change in mood.

Allergic (hypersensitivity) reactions such as rash, hives, swelling of the face, lips and throat are possible side effects of ONGLYZA. If you have these symptoms, tell your physician or pharmacist.

Tell your physician or pharmacist if you develop any unusual side effects, or if any of the above side effects do not go away or gets worse.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very rare	Allergic reaction, hives, swelling of face, lips or throat		X	X
Uncommon	Rash	X		

This is not a complete list of side effects. For any unexpected effects while taking ONGLYZA, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep ONGLYZA well out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing.

The Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: www.bmscanada.ca and www.astrazeneca.ca or by contacting Bristol-Myers Squibb Canada, at 1-866-463-6267.

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