ONGLYZA™
2.5 mg and 5 mg
Saxagliptin HCl
Film-coated tablets

Qualitative and quantitative composition
Each film-coated tablet of saxagliptin (ONGLYZA) contains 5 mg or 2.5 mg of saxagliptin free base (as saxagliptin hydrochloride).

Pharmaceutical form
2.5 mg ONGLYZA tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with "2.5" printed on one side and "4214" printed on the reverse side, in blue ink

5 mg ONGLYZA tablets are pink, biconvex, round, film-coated tablets with "5" printed on one side and "4215" printed on the reverse side, in blue ink.

Therapeutic indication
Add-on combination therapy:
ONGLYZA is indicated in adult patient with type 2 diabetes mellitus to improve glycaemic control:
- in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control.
- in combination with a sulphonylurea, when the sulphonylurea alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.
- in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate.
- in combination with insulin (with or without metformin), when this regime alone, with diet and exercise, does not provide adequate glycaemic control

Posology and method of administration
Posology
Add-on combination therapy
The recommended dose of ONGLYZA is 5 mg once daily as add-on combination therapy with metformin, insulin, a thiazolidinedione or a sulphonylurea.

The safety and efficacy of saxagliptin as triple oral therapy in combination with metformin and a thiazolidinedione, or with metformin and a sulphonylurea, has not been established.

Special populations
Renal impairment
No dose adjustment is recommended for patients with mild renal impairment.

The dose of ONGLYZA should be reduced to 2.5 mg once daily in patients with moderate renal impairment. Clinical study experience with ONGLYZA in patients with severe renal impairment or patient with end-stage renal disease (ESRD) requiring haemodialysis is limited. Therefore, use of ONGLYZA is not recommended in this patient population (see section 'Special warnings and precautions for use and Pharmacokinetic properties). Because the dose of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA, and, in keeping with routine care, renal assessment should be done periodically thereafter (*see section 'Special warnings and precautions for use' and 'Pharmacokinetic properties'*).

Hepatic impairment
No dose adjustment is necessary for patients with mild or moderate hepatic impairment (see section *Pharmacokinetic properties*). Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment (see section *Special warnings and precautions for use*).

Elderly (≥65 years)
No dose adjustment is recommended based solely on age. Experience in patients aged 75 years and older is very limited and caution should be exercised when treating this population (see also sections *Special warnings and precautions for use*, *Pharmacodynamic properties* and *Pharmacokinetic properties*).

Paediatric population
ONGLYZA is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Method of administration
ONGLYZA can be taken with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Contraindications
Hypersensitivity to the active substance or to any of the excipient or history of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any dipeptidyl peptidase-4 (DPP4) inhibitor *(see sections 'Special warnings and precautions for use', and 'Undesirable effects')*

Special warnings and precautions for use
General
ONGLYZA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. ~~Saxagliptin has not been studied in combination with insulin.~~

Onglyza is not a substitute for insulin in insulin-requiring patients.

Pancreatitis
In post-marketing experience there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute

pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of saxagliptin. If pancreatitis is suspected, ONGLYZA and other potentially suspect medicinal products should be discontinued.(*see sections 'Undesirable effects'*)

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the incidence of adjudicated pancreatitis events was 0.3% in both ONGLYZA-treated patients and placebo-treated patients in the intent-to-treat population (see *Clinical experience*).

Renal impairment
Clinical study experience with saxagliptin in patients with ~~moderate to~~ severe renal impairment is limited. Therefore, use of ONGLYZA is not recommended in this patient population (see sections *Posology and method of administration* and *Pharmacokinetic properties*).

Hepatic impairment
Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment (see section *Posology and method of administration*).

Use with medicinal products known to cause hypoglycaemia
Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, a lower dose of sulphonylurea or insulin may be required to reduce the risk of hypoglycaemia when used in combination with ONGLYZA.

Hypersensitivity reactions
ONGLYZA should not be used in patients who have had any serious hypersensitivity reaction to a dipeptidyl peptidase 4 (DPP4) inhibitor. During postmarketing experience, the following adverse reactions have been reported with use of saxagliptin: serious hypersensitivity reactions, including anaphylaxis and angioedema. If a serious hypersensitivity reaction to saxagliptin is suspected, discontinue ONGLYZA, assess for other potential causes for the event, and institute alternative treatment for diabetes (see sections *Contraindications* and *Undesirable Effects*).

Elderly patients
Experience in patients aged 75 years and older is very limited and caution should be exercised when treating this population (see sections *Pharmacodynamic properties* and *Pharmacokinetic properties*).

Of the 16,492 patients randomized in the SAVOR trial, 8561 (51.9%) patients were 65 years and over and 2330 (14.1%) were 75 years and over. The number of subjects treated with ONGLYZA in the SAVOR study that were 65 years and over was 4290 and the number of subjects that were 75 years and over was 1169.

Skin disorders
Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies (see section *Preclinical safety data*). Although skin lesions

were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications. Post marketing reports of rash have been described in the DPP4 inhibitor class. Rash is also noted as an adverse event (AE) for ONGLYZA (section *Undesirable effects*). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Cardiac failure

In the SAVOR trial an increase in the rate of hospitalization for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established. Caution is warranted if Onglyza is used in patients who have known risk factors for hospitalization for heart failure, such as a history of heart failure or moderate to severe renal impairment.~~29~~ Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms. (See *Cardiovascular Safety Study*)

Immunocompromised patients

Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the ONGLYZA clinical program. Therefore, the efficacy and safety profile of saxagliptin in these patients has not been established.

Use with potent CYP 3A4 inducers

Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may reduce the glycaemic lowering effect of ONGLYZA (see section *Interaction with other medicinal products and other forms of interaction*).

Lactose

The tablet contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Arthralgia

Joint pain, which may be severe, has been reported in postmarketing reports for DPP4 inhibitors.30 Patients experienced relief of symptoms after discontinuation of the medication and some experienced recurrence of symptoms with reintroduction of the same or another DPP4 inhibitor. Onset of symptoms following initiation of drug therapy may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of drug therapy should be individually assessed. (See Adverse Reactions)

Interactions with other medicinal products and other forms of interaction

Clinical data described below suggest that the risk for clinically meaningful interactions with co-administered medicinal products is low.

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4. In studies conducted in healthy subjects, neither the pharmacokinetics of saxagliptin and its major

metabolite, were meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine. In addition, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem or ketoconazole.

Concomitant administration of saxagliptin with the moderate inhibitor of CYP3A4/5 diltiazem, increased the C_{max} and AUC of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44 and 34%, respectively.

Concomitant administration of saxagliptin with the potent inhibitor of CYP3A4/5 ketoconazole, increased the C_{max} and AUC of saxagliptin by 62% and 2.5-fold, respectively, and the corresponding values for the active metabolite were decreased by 95% and 88%, respectively.

Concomitant administration of saxagliptin with the potent CYP3A4/5 inducer rifampicin, reduced C_{max} and AUC of saxagliptin by 53% and 76%, respectively. The exposure of the active metabolite and the plasma DPP4 activity inhibition over a dose interval were not influenced by rifampicin (*see section 'Special warnings and precautions for use'*).

The co-administration of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) have not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycaemic control should be carefully assessed when saxagliptin is used concomitantly with a potent CYP3A4 inducer.

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of saxagliptin have not been specifically studied.

Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of saxagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section *Preclinical safety data*). The potential risk for humans is unknown. ONGLYZA should not be used during pregnancy unless clearly necessary.

Lactation

It is unknown whether saxagliptin is excreted in human breast milk. Animal studies have shown excretion of saxagliptin and/or metabolite in milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy to the woman.

Fertility

The effect of saxagliptin on fertility in humans has not been studied. Effects on fertility were observed in male and female rats at high doses producing overt signs of toxicity (see section *Preclinical safety data*).

Effects on ability to drive and use machines

ONGLYZA may have a negligible influence on the ability to drive and use machines.

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness has been reported with saxagliptin.

Undesirable effects

Clinical experience

In randomized, controlled, double-blind clinical trials, over 17.000 patients with type 2 diabetes have been treated with ONGLYZA.

Adverse reactions associated with ONGLYZA in the SAVOR trial

The overall incidence of adverse events in patients treated with ONGLYZA in this trial was similar to placebo (72.5% versus 72.2%, respectively).
In the SAVOR trial, the incidence of adjudicated pancreatitis events was 0.3% in both ONGLYZA -treated patients and placebo-treated patients in the intent-to-treat population.

The incidence of hypersensitivity reactions was 1.1% in both ONGLYZA -treated patients and placebo-treated patients.

Hypoglycemia
In the SAVOR trial, the overall incidence of reported hypoglycemia (recorded in daily patient diaries) was 17.1% in ONGLYZA-treated patients and 14.8% in placebo-treated patients.

The percent of subjects with reported on-treatment events of major hypoglycemia (defined as an event that required assistance of another person) was higher in the saxagliptin group than in the placebo group (2.1% and 1.6%, respectively).

The increased risk of overall hypoglycemia and major hypoglycemia observed in the saxagliptin-treated group occurred primarily in subjects treated with a sulfonylurea at baseline and not in subjects on insulin or metformin monotherapy at baseline.

The increased risk of overall and major hypoglycemia was primarily observed in subjects with A1C <7% at baseline.

Summary of the safety profile
There were 4,148 patients with type 2 diabetes, including 3,021 patients treated with ONGLYZA, randomised in six double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control.

In a pooled analysis, the overall incidence of adverse events in patients treated with saxagliptin 5 mg was similar to placebo. Discontinuation of therapy due to adverse events was higher in patients who received saxagliptin 5 mg as compared to placebo (3.3% as compared to 1.8%).

Tabulated list of adverse reactions
Adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients treated with saxagliptin 5 mg and more commonly than in patients treated with placebo or that were reported in ≥2% of patients treated with saxagliptin 5 mg and ≥1% more frequently compared to placebo are shown in Table 1.

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as Very common (≥ 1/10), Common (≥ 1/100 to <1/10), Uncommon (≥ 1/1,000 to 1/100), Rare (≥ 1/10,000 to 1/1,000), or Very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 Frequency of adverse reactions by system organ class

System organ class Adverse Reaction	**Saxagliptin with metformin**[1]	**Saxagliptin with a sulphonylurea (glibenclamide)**	**Saxagliptin with a thiazolidinedione**
Infections and infestations			
Upper respiratory infection	Common	Common	Common
Urinary tract infection	Common	Common	Common
Gastroenteritis	Common	Common	Common
Sinusitis	Common	Common	Common
Nasopharyngitis	Common[2]		
Immune System disorders			
Hypersensitivity reactions†‡	Uncommon	Uncommon	Uncommon
Anaphylactic reactions including anaphylactic shock†‡	Rare	Rare	Rare
Metabolism and nutrition disorders			
Hypoglycaemia		Very common[3]	
Dyslipidemia		Uncommon	
Hypertri-Glyceridemia		Uncommon	
Nervous system disorders			
Dizziness			

Headache	Common	Common	Common
Gastrointestinal disorders			
Abdominal pain†	Common	Common	Common
Diarrhoea[4]	Common	Common	Common
Dyspepsia	Common		
Flatulence			
Gastritis	Common		
Nausea†	Common	Common	Common
Vomiting	Common	Common	Common
Pancreatitis†	Uncommon	Uncommon	Uncommon
Constipation†	Not known	Not known	Not known
Skin and subcutaneous tissue disorders			
Rash†	Common	Common	
Dermatitis†	Uncommon	Uncommon	Uncommon
Pruritus†	Uncommon	Uncommon	Uncommon
Urticaria†	Uncommon	Uncommon	Uncommon
Angioedema†‡	Rare	Rare	Rare
Musculoskeletal and connective tissue disorders			
Arthralgia*	Uncommon		
Myalgia[5]	Common		
Reproductive system and breast disorders			
Erectile dysfunction	Uncommon		

General disorders and administration site conditions		
Fatigue	Uncommon	
Oedema peripheral		Common[4]

[1]Includes saxagliptin in add-on to metformin and initial combination with metformin.
[2]Only in the initial combination therapy.
[3]There was no statistically significant difference compared to placebo. The incidence of confirmed hypoglycaemia was uncommon for ONGLYZA 5 mg (0.8%) and placebo (0.7%).
[4] The incidence of diarrhea was 4.1% (36/882) in the saxagliptin 5 mg group and 6.1% (49/799) in the placebo group.
[5]As initial combination with metformin, myalgia is reported as uncommon
†Adverse reactions were identified through postmarketing surveillance
‡ See sections 4.3 and 4.4.
*Also reported during postmarketing surveillance (see section 4.4).

Description of selected adverse reactions
In addition to the adverse reactions described above, adverse events reported regardless of causal relationship to the medicinal product and occurring more commonly in patients treated with ONGLYZA include hypersensitivity (0.6% vs. 0%) and rash (1.4% vs. 1.0%) as compared with placebo.

Adverse events, considered by the investigator to be at least possibly drug-related and reported in at least two more patients treated with saxagliptin 5 mg compared to control, are described below by treatment regimen.

As monotherapy: dizziness (common) and fatigue (common).

As add-on to metformin: dyspepsia (common) and myalgia (common).

As add-on to sulphonylurea (glibenclamide): fatigue (uncommon), dyslipidemia (uncommon) and hypertriglyceridemia (uncommon).

As initial combination with metformin: gastritis (common), arthralgia (uncommon), myalgia (uncommon), and erectile dysfunction (uncommon).

When used as add-on to insulin (with or without metformin), the overall incidence of reported hypoglycaemia was 18.4% for Onglyza 5 mg and 19.9% for placebo

Adverse reactions from spontaneous reporting
During postmarketing experience, the following adverse reactions have been reported with use of saxagliptin: acute pancreatitis, arthralgia and hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency (see sections *Contraindications* and *Special warnings and precautions for use*).

Laboratory tests
Across clinical studies, the incidence of laboratory adverse events was similar in patients treated with saxagliptin 5 mg compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2,200 cells/μl, a mean decrease of approximately 100 cells/μl relative to placebo was observed in the placebo-controlled-pooled analysis. Mean absolute lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The clinical significance of this decrease in lymphocyte count relative to placebo is not known.

In the SAVOR trial, decreased lymphocyte counts were reported in 0.5% of ONGLYZA-treated patients and 0.4% of placebo-treated patients.

Overdose
ONGLYZA has been shown to be safe and well-tolerated with no clinically meaningful effect on QTc interval or heart rate at oral doses up to 400 mg daily for 2 weeks (80 times the recommended dose). 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 can be removed by haemodialysis (23% of dose over 4 hours).

Pharmacological properties
Pharmacodynamic properties
Pharmacotherapeutic group; Drug used in diabetes. Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH03

Mechanism of action
Saxagliptin is a highly potent (Ki: 1.3 nM), selective, reversible, competitive, DPP-4 inhibitor. In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load, this DPP-4 inhibition resulted in a 2-to 3-fold increase in circulating levels of active incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic beta-cells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes.

Clinical safety and efficacy

A total of 4,148 patients with type 2 diabetes, including 3,021 patients treated with, saxagliptin were randomised in 6 double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control. In these studies 634 patients were 65 years and older, while 59 patients were 75 years and older. Treatment with saxagliptin 5 mg once daily produced clinically relevant and statistically significant improvements in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG) compared to placebo in monotherapy, in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea, and in combination with a thiazolidinedione (see Table 2). There was also no apparent change in body weight associated with saxagliptin. Reductions in HbA1c were seen across subgroups including gender, age, race, and baseline body mass index (BMI) and higher baseline HbA1c was associated with a greater adjusted mean change from baseline with saxagliptin.

Saxagliptin add-on to metformin therapy

An add-on to metformin placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with metformin in patients with inadequate glycaemic control (HbA1c 7-10%) on metformin alone. Saxagliptin (n=186) provided significant improvements in HbA1c, FPG and PPG compared to placebo (n=175). Improvements in HbA1c, PPG, and FPG following treatment with saxagliptin 5 mg plus metformin were sustained up to Week 102. The HbA1c change for saxagliptin 5 mg plus metformin (n=31) compared to placebo plus metformin (n=15) was -0.8% at Week 102.

Saxagliptin add-on to metformin compared with SU add-on to metformin

A 52-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (428 patients) compared with sulphonylurea (glipizide, 5 mg titrated as needed to 20 mg, mean dose of 15 mg) in combination with metformin (430 patients) in 858 patients with inadequate glycaemic control (HbA1c 6.5%-10%) on metformin alone. The mean metformin dose was approximately 1900 mg in each treatment group. After 52 weeks, the saxagliptin and glipizide groups had similar mean reductions from baseline in HbA1c in the per-protocol analysis (-0.7% vs. -0.8%, respectively, mean baseline HbA1c of 7.5% for both groups). The intent-to-treat analysis showed consistent results. The reduction in FPG was slightly less in the saxagliptin-group and there were more discontinuations (3.5% vs. 1.2%) due to lack of efficacy based on FPG criteria during the first 24 weeks of the study. Saxagliptin also resulted in a significantly lower proportion of patients with hypoglycaemia, 3% (19 events in 13 subjects) vs. 36.3% (750 events in 156 patients) for glipizide. Patients treated with saxagliptin exhibited a significant decrease from baseline in body weight compared to a weight gain in patients administered glipizide (-1.1 vs. +1.1 kg).

Saxagliptin add-on to metformin compared with sitagliptin add-on to metformin

An 18-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (403 patients), compared with sitagliptin 100 mg in combination with metformin (398 patients) in 801 patients with inadequate glycaemic control on metformin alone. After 18 weeks, saxagliptin was non-inferior to sitagliptin in mean reduction from baseline in HbA1c in both the per-protocol and the full analysis sets . The reductions

from baseline in HbA1c respectively for saxagliptin and sitagliptin in the primary per-protocol analysis were -0.5% (mean and median) and -0.6% (mean and median). In the confirmatory full analysis set, mean reductions were -0.4% and -0.6% respectively for saxagliptin and sitagliptin, with median reductions of -0.5% for both groups.

~~*Saxagliptin in combination with metformin as initial therapy*~~
~~A 24-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin as initial combination therapy in treatment-naïve patients with inadequate glycaemic control (HbA1c 8-12%). Initial therapy with the combination of saxagliptin 5 mg plus metformin (n=306) provided significant improvements in HbA1c, FPG and PPG compared to with either saxagliptin (n=317) or metformin alone (n=313) as initial therapy. Reductions in HbA1c from baseline to Week 24 were observed in all evaluated subgroups defined by baseline HbA1c, with greater reductions observed in patients with a baseline HbA1c ≥10% (see Table 2). Improvements in HbA1c, PPG and FPG following initial therapy with saxagliptin 5 mg plus metformin were sustained up to Week 76. The HbA1c change for saxagliptin 5 mg plus metformin (n=177) compared to metformin plus placebo (n=147) was -0.5% at Week 76.~~

Saxagliptin add-on combination therapy with insulin (with or without metformin)
A total of 455 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with a stable dose of insulin (baseline mean: 54.2 Units) in patients with inadequate glycaemic control (HbA1c ≥7.5% and ≤11%) on insulin alone (n=141) or on insulin in combination with a stable dose of metformin (n=314). Saxagliptin 5 mg add-on to insulin with or without metformin provided significant improvements after 24 weeks in HbA1c and PPG compared with placebo add-on to insulin with or without metformin. Similar HbA1c reductions versus placebo were achieved for patients receiving saxagliptin 5 mg add-on to insulin regardless of metformin use (−0.4% for both subgroups). Improvements from baseline HbA1c were sustained in the saxagliptin add-on to insulin group compared to the placebo add-on to insulin group with or without metformin at Week 52. The HbA1c change for the saxagliptin group (n=244) compared to placebo (n=124) was -0.4% at Week 52.

Saxagliptin add-on to glibenclamide therapy
An add-on placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with glibenclamide in patients with inadequate glycaemic control at enrolment (HbA1c 7.5-10%) on a sub-maximal dose of glibenclamide alone. Saxagliptin in combination with a fixed, intermediate dose of a sulphonylurea (glibenclamide 7.5 mg) was compared to titration to a higher dose of glibenclamide (approximately 92% of patients in the placebo plus glibenclamide group were up-titrated to a final total daily dose of 15 mg). Saxagliptin (n=250) provided significant improvements in HbA1c, FPG and PPG compared to titration to a higher dose of glibenclamide ~~(n=264).Improvements in HbA1c and PPG following treatment with saxagliptin 5 mg were sustained up to Week 76. The HbA1c change for saxagliptin 5 mg (n=56) compared to uptitrated glibenclamide plus placebo (n=27) was -0.7% at Week 76~~

Saxagliptin add-on to thiazolidinedione therapy

A placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with a thiazolidinedione (TZD) in patients with inadequate glycaemic control (HbA1c 7-10.5%) on TZD alone.

~~Saxagliptin (n=183) provided significant improvements in HbA1c, FPG and PPG compared to placebo (n=180). Improvements in HbA1c, PPG and FPG following treatment with saxagliptin 5 mg were sustained up to Week 76. The HbA1c change for saxagliptin 5 mg (n=82) compared to TZD plus placebo (n=53) was -0.9% at Week 76.~~

Patients with renal impairment

A 12-week, multi-centre, randomised, double-blind, placebo-controlled study was conducted to evaluate the treatment effect of saxagliptin 2.5 mg once daily compared with placebo in 170 patients (85 patients on saxagliptin and 85 on placebo) with type 2 diabetes (HbA1c 7.0-11%) and renal impairment (moderate [N=90]; severe [N=41]; or ESRD [N=39]). In this study, 98.2% of the patients were treated with other antihyperglycaemic medication (75.3% on insulin and 31.2% on oral antihyperglycaemic drugs; some received both). Saxagliptin significantly decreased HbA1c compared with placebo; the HbA1c change for saxagliptin was -0.9% at Week 12 (HbA1c change of -0.4% for placebo). Improvements in HbA1c following treatment with saxagliptin 2.5 mg were sustained up to Week 52, however the number of patients who completed 52 weeks without modification of other antihyperglycaemic medications was low (26 subjects in the saxagliptin group versus 34 subjects in the placebo group). The incidence of confirmed hypoglycaemic events was somewhat higher in the saxagliptin group (9.4%) versus placebo group (4.7%) although the number of subjects with any hypoglycaemic event did not differ between the treatment groups. There was no adverse effect on renal function as determined by estimated glomerular filtration rate or CrCL at Week 12 and Week 52.

Table 2 Key efficacy results of ONGLYZA 5 mg per day in placebo-controlled add-on combination therapy trials

	Mean baseline HbA_{1c} (%)	**Mean change[2] from baseline HbA_{1c} (%) at Week 24**	**Placebo-corrected mean change in HbA_{1c} (%) at Week 24 (95% CI)**
ADD-ON/COMBINATION STUDIES			
• Study CV181014: add-on to metformin (n=186)	8.1	-0.7	-0.8 (-1.0, -0.6)[3]
• Study CV181040: add-on to SU[1] (n=250)	8.5	-0.6	-0.7 (-0.9, -0.6)[3]
• Study CV181013: add-on to TZD (n=183)	8.4	-0.9	-0.6 (-0.8, -0.4)[3]
• Study CV181039: initial combination with metformin[4]			
Overall population (n=306)	9.4	-2.5	-0.5 (-0.7, -0.4)[5]
Baseline HbA1c ≥10% strata (n=107)	10.8	-3.3	-0.6 (-0.9, -0.3)[6]

• Study CV181057: add-on to insulin (+/-metformin) Overall population (n=300)	8.7	-0.7	-0.4 (-0.6, -0.2)[3]

•

n=Randomized patients (primary efficacy-intention-to-treat analysis) with data available

[1]Placebo group had uptitration of glibenclamide from 7.5 to 15 mg total daily dose.
[2] Adjusted mean change from baseline adjusted for baseline value (ANCOVA).
[3] p<0.0001 compared to placebo.
[4] Metformin was uptitrated from 500 to 2000 mg per day as tolerated.
[5] Mean HbA1c change is the difference between the saxagliptin+metformin and metformin alone groups (p<0.0001).
[6] Mean HbA1c change is the difference between the saxagliptin+metformin and metformin alone groups.

Cardiovascular safety
The SAVOR trial included 8240 patients treated with ONGLYZA ~~5 mg or 2.5 mg~~ once daily and 8173 patients on placebo. The mean duration of ONGLYZA exposure regardless of interruptions was 1.8 years. A total of 3698 subjects (45%) were treated with ONGLYZA for between 2 and 3 years.

The primary safety and efficacy endpoint was a composite endpoint consisting of the time-to first occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke.

The primary safety objective of this trial was to establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI or non-fatal ischemic stroke observed with saxagliptin to that observed in the placebo group was <1.3.

The primary efficacy objective was to determine, as a superiority assessment, whether treatment with saxagliptin, compared with placebo when added to current background therapy, resulted in a significant reduction in the primary MACE endpoint.

The first secondary efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of MACE plus hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary revascularization (MACE plus). The next secondary efficacy endpoint was to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM would result in a reduction of all-cause mortality.

SAVOR established the CV safety of saxagliptin, as CV risk (CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke) was not increased in patients with T2DM compared to placebo when added to current background therapy (HR 1.00; 95% CI: 0.89, 1.12; P<0.001 for noninferiority).

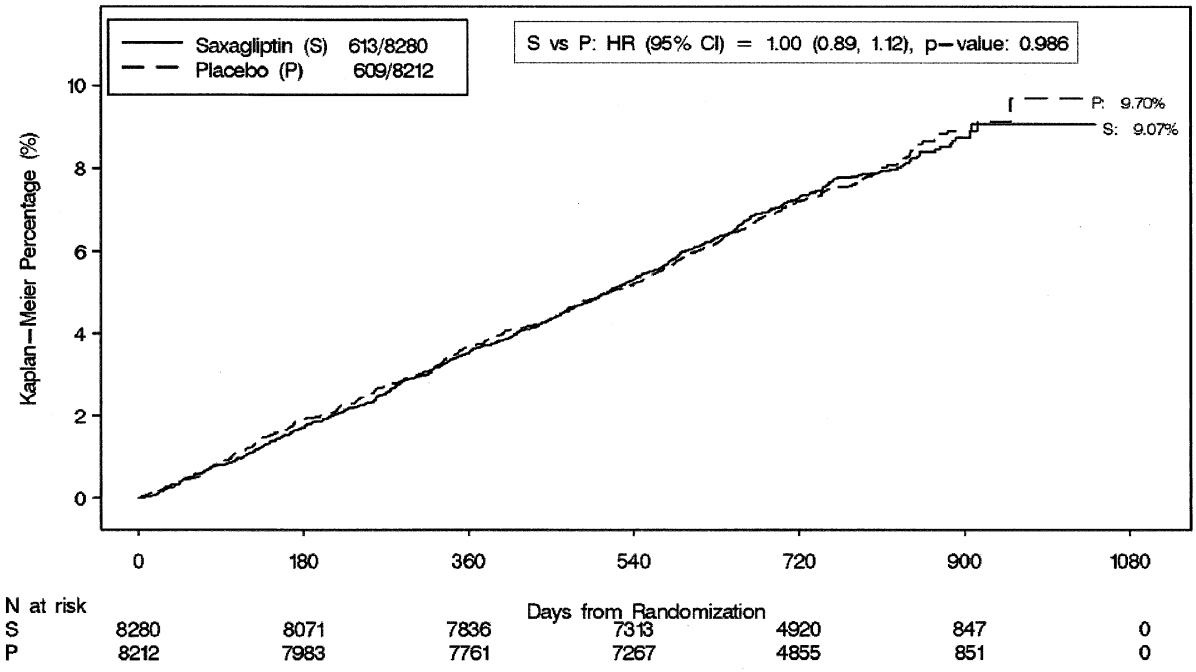
The primary efficacy endpoint did not demonstrate a statistically significant difference in major adverse CV events for saxagliptin compared to placebo when added to current background therapy in patients with T2DM.

Table 3 Primary and Secondary Clinical Endpoints by Treatment Group in the SAVOR Study*

Endpoint	ONGLYZA (N=8280)		Placebo (N=8212)		Hazard Ratio (95% CI)†
	Subjects with events n (%)	Event rate per 100 patient-yrs	Subjects with events n (%)	Event rate per 100 patient-yrs	
Primary composite endpoint: MACE	613 (7.4)	3.76	609 (7.4)	3.77	1.00 (0.89, 1.12)‡,§
Secondary composite endpoint: MACE plus	1059 (12.8)	6.72	1034 (12.6)	6.60	1.02 (0.94, 1.11)¶
All-cause mortality	420 (5.1)	2.50	378 (4.6)	2.26	1.11 (0.96, 1.27)¶

* Intent-to-treat population
† Hazard ratio adjusted for baseline renal function category and baseline CVD risk category.
‡ P-value <0.001 for non-inferiority (based on HR <1.3) compared to placebo.
§ P-value = 0.99 for superiority (based on HR <1.0) compared to placebo.
¶ Significance not tested.

Figure 7 Cumulative percent of time to first CV event for primary composite endpoint*



* Intent-to-treat population

Events accumulated consistently over time, and the event rates for TRADEMARK and placebo did not diverge notably over time.

One component of the secondary composite endpoint, hospitalization for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance (ie, without adjustment for testing of multiple endpoints) favouring placebo [HR = 1.27; (95% CI 1.07, 1.51); P = 0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at higher risk for hospitalization for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.

No increased risk for the primary endpoint was observed between saxagliptin and placebo in any of the following subgroups: CVD, multiple risk factors for CVD, mild, moderate, or severe renal impairment, age, gender, race, region, duration of type 2 diabetes, history of heart failure, baseline A1C, albumin/creatinine ratio, baseline antidiabetic medication, or baseline use of statins, aspirin, ACE inhibitors, ARBs, beta-blockers, or antiplatelet medications.

Despite active management of concomitant antidiabetic therapy in both study arms, mean A1C levels were lower in the saxagliptin group compared to the placebo group at Year 1 (7.6% versus 7.9%, difference of –0.35% [95% CI: –0.38, –0.31]) and at Year 2 (7.6% versus 7.9%, difference of –0.30% [95% CI: –0.34, –0.26]). The proportions of subjects with A1C <7% in the saxagliptin group compared to the placebo group were 38% versus 27% at Year 1 and 38% versus 29% at Year 2.

Compared to placebo, saxagliptin resulted in less need for the initiation of new or increases in current oral diabetes medications or insulin. The improvements in A1C and the proportion of subjects reaching A1C targets among saxagliptin-treated subjects were observed despite lower rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin compared with placebo.

Pharmacokinetic properties

The pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption

Saxagliptin was rapidly absorbed after oral administration in the fasted state, with maximum plasma concentrations (C_{max}) of saxagliptin and its major metabolite attained within 2 and 4 hours (T_{max}), respectively. The C_{max} and AUC values of saxagliptin and its major metabolite increased proportionally with the increment in the saxagliptin dose, and this dose-proportionality was observed in doses up to 400 mg. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC 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%.

The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site.

Interaction with food
Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with food (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 negligible. 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.

Biotransformation
The biotransformation 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.

Elimination
The mean plasma terminal half-life ($t_{1/2}$) values for saxagliptin and its major metabolite are 2.5 hours and 3.1 hours respectively, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. 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 faeces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed medicinal product from the gastrointestinal tract.

Linearity
The C_{max} and AUC of saxagliptin and its major metabolite increased proportionally to the saxagliptin dose. No appreciable accumulation of either saxagliptin or its major metabolite 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.

Special populations

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a 10 mg oral dose of saxagliptin in subjects 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 (based on the Cockcroft-Gault formula) as mild (>50 to ≤80 ml/min), moderate (≥30 to ≤50 ml/min), or severe (≤30 ml/min), as well as patients with ESRD on haemodialysis.

The degree of renal impairment did not affect the Cmax of saxagliptin or its major metabolite. In subjects with mild renal impairment, the mean AUC values of saxagliptin and its major metabolite were 1.2- and 1.7- fold higher, respectively, than mean AUC values in subjects with normal renal function. Because increases of this magnitude are not clinically relevant, dose adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment or in subjects with ESRD on haemodialysis, 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. The dose of ONGLYZA should be reduced to 2.5 mg once daily in patients with moderate ~~or severe~~ renal impairment (see sections 'Posology and method of administration' and 'Special warnings and precautions for use').

Hepatic impairment

In subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to BMS-510849 were 22%, 7%, and 33% lower, respectively, than those observed in healthy subjects.

Elderly patients (≥65 years)

Elderly (65-80 years) had about 60% higher saxagliptin AUC than young patients (18-40 years). This is not considered clinically meaningful, therefore, no dose adjustment for ONGLYZA is recommended on the basis of age alone.

Preclinical safety data

In cynomolgus monkeys saxagliptin produced reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) at doses ≥3 mg/kg/day. The no effect level (NOEL) for the lesions is 1 and 2 times the human exposure of saxagliptin and the major metabolite respectively, at the recommended human dose of 5 mg/day (RHD). The clinical relevance of the skin lesions is not known, however clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.
Immune related findings of minimal, nonprogressive, lymphoid hyperplasia in spleen, lymph nodes and bone marrow with no adverse sequelae have been reported in all species tested at exposures starting from 7 times the RHD.

Saxagliptin produced gastrointestinal toxicity in dogs, including bloody/mucoid faeces and enteropathy at higher doses with a NOEL 4 and 2 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD.

Saxagliptin was not genotoxic in a conventional battery of genotoxicity studies *in vitro* and *in vivo*. No carcinogenic potential was observed in two-year carcinogenicity assays with mice and rats.

Effects on fertility were observed in male and female rats at high doses producing overt signs of toxicity. Saxagliptin was not teratogenic at any doses evaluated in rats or rabbits. At high doses in rats, saxagliptin caused reduced ossification (a developmental delay) of the foetal pelvis and decreased foetal body weight (in the presence of maternal toxicity), with a NOEL 303 and 30 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (NOEL 158 and 224 times the human exposure for saxagliptin and the major metabolite, respectively at RHD). In a pre- and postnatal developmental study in rats, saxagliptin caused decreased pup weight at maternally toxic doses, with NOEL 488 and 45 times the human exposure for saxagliptin and the major metabolite, respectively at RHD. The effect on offspring body weights were noted until postnatal day 92 and 120 in females and males, respectively.

List of excipients

Each film-coated tablet of ONGLYZA contains 5 mg or 2.5 mg of saxagliptin free base (as saxagliptin hydrochloride) and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

Incompatibilities

None

Shelf life

Please refer to expiry date on outer carton.

Special precautions for storage

Store below 30°C.

Pack size

2.5 mg ONGLYZA tablet: Box of 2 blisters @ 14 film-coated tablets
(Reg. No: DKIXXXXXXXXX)
5 mg ONGLYZA tablet: Box of 2 blisters @ 14 film-coated tablets
(Reg. No.: DKI1196300817A1)

HARUS DENGAN RESEP DOKTER

Manufactured by Manufactured by AstraZeneca Pharmaceuticals LP, Mount Vernon, IN 47620, USA

Packaged by Bristol-Myers Squibb S.r.l. 03012 Anagni, Italy
For AstraZeneca UK Limited, Macclesfield, Cheshire, SK10 2NA, United Kingdom

Imported by
PT AstraZeneca Indonesia, Cikarang, Bekasi – Indonesia

Date of revision of text
As on approval date
GEL Ref.:

Onglyza is a trademark of Astrazeneca

Informasi untuk Pasien
ONGLYZA™ 2.5 & 5 mg
Tablet Salut Selaput
Saxagliptin HCl

Bacalah seluruh isi leaflet ini dengan seksama sebelum anda mulai menggunakan obat ini karena leaflet ini berisi informasi penting bagi anda.

- Simpan leaflet ini, anda mungkin memerlukannya di kemudian hari.
- Apabila anda memiliki pertanyaan lebih lanjut, hubungi dokter, apoteker, atau perawat anda.
- Obat ini hanya diresepkan untuk anda. Dilarang memberikan obat ini untuk orang lain. Hal ini dapat membahayakan orang lain, bahkan jika tanda penyakit yang mereka derita sama dengan penyakit anda.
- Apabila anda mengalami efek samping, komunikasikan dengan dokter, apoteker atau perawat anda. Hal ini termasuk efek samping yang mungkin timbul yang tidak terdaftar dalam leaflet ini.

Informasi yang terkandung dalam leaflet ini:

1. Onglyza dan kegunaannya

Onglyza mengandung zat aktif saxagliptin, yang tergolong dalam kelompok obat antidiabetik oral. Obat ini bekerja membantu mengontrol kadar gula dalam darah anda.

Onglyza digunakan pada pasien dewasa diatas usia 18 tahun dengan diabetes tipe 2, apabila penyakitnya tidak dapat dikontrol dengan menggunakan satu jenis obat antidiabetik oral, diet, dan aktivitas fisik. Onglyza digunakan dengan dikombinasikan dengan insulin maupun obat-obatan antidiabetik oral lainnya seperti metformin, golongan sulfonylurea, dan golongan thiazolidinedione, apabila dokter menganggap pengobatan dengan obat – obat tersebut secara tunggal disertai dengan diet dan olahraga sudah tidak adekuat mengontrol gula darah anda.

Sangat penting untuk menjalankan anjuran diet dan aktivitas fisik yang diberikan oleh dokter atau perawat anda.

2. Hal yang perlu Anda ketahui sebelum mengkonsumsi Onglyza

Jangan gunakan Onglyza :

- Apabila anda memiliki alergi terhadap saxagliptin atau bahan lain yang terkandung dalam obat ini (*lihat bagian isi kemasan obat dan informasi lainnya*).
- Apabila anda memiliki reaksi alergi berat terhadap obat-obatan lain dalam jenis yang sama untuk mengontrol kadar gula darah anda.

Peringatan dan pencegahan

Komunikasikan terhadap dokter atau apoteker anda sebelum menggunakan Onglyza apabila:

- Apabila menggunakan insulin. Onglyza tidak dapat digunakan untuk menggantikan insulin

- Apabila anda mengidap diabetes tipe 1 (tubuh anda tidak dapat memproduksi insulin) atau ketoasidosis diabetikum (sebuah komplikasi diabetes dengan kadar gula darah yang sangat tinggi, penurunan berat badan drastis, mual, atau muntah). Onglyza sebaiknya tidak digunakan pada keadaan-keadaan ini
- Apabila anda mengidap atau pernah mengalami penyakit pankreas
- Apabila anda menggunakan insulin atau obat antidiabetik yang termasuk dalam golongan 'sulfonilurea' (contohnya : glibencamide, glipizide, gliclazide, gliquidone, glimepiride), dokter anda mungkin dapat mengurangi dosis insulin atau sulfonilurea anda apabila anda menggunakannya bersamaan dengan Onglyza untuk menghindari kadar gula darah yang rendah.
- Apabila anda memiliki kondisi yang melemahkan pertahanan tubuh anda terhadap infeksi, seperti AIDS, atau anda mengkonsumsi obat-obatan yang anda minum setelah transplantasi organ.
- Apabila anda mengalami kondisi gagal jantung atau faktor risiko gagal jantung seperti penyakit ginjal. Dokter anda akan memberitahukan anda mengenai tanda dan gejala gagl jantung. Anda harus segera menghubungi dokter, apoteker, atau perawat anda apabila anda mengalami gejala-gejala tersebut. Gejala-gejala ini meliputi, namun tidak terbatas pada, sesak nafas yang bertambah berat, kenaikan berat badan dan pembengkakkan pada kedua kaki (edema pedalis).
- Apabila anda mengalami gangguan ginjal derajat sedang atau berat, anda akan memerlukan Onglyza dalam dosis yang lebih rendah. Apabila anda menjalani hemodialisis, maka Onglyza tidak direkomendasikan bagi anda.
- Apabila anda mengalami gangguan liver derajat sedang atau berat. Apabila anda mengalami gangguan liver derajat berat, maka Onglyza tidak direkomendasikan bagi anda.

Lesi kulit diabetik merupakan komplikasi yang cukup sering terjadi. Ruam seringkali terlihat pada penggunaan Onglyza (lihat *Efek samping yang mungkin terjadi*) dan pada penggunaan beberapa obat antidiabetik lain yang sekelas dengan Onglyza. Anda dianjurkan untuk mengikuti rekomendasi perawatan kulitdan kaki yang diberikan dokter atau perawat anda.

Anak-anak dan remaja
Onglyza tidak direkomendasikan untuk anak dan remaja di bawah usia 18 tahun. Keamanan dan keefektifan obat ini pada anak-anak dan remaja di bawah usia 18 tahun tidak diketahui.

Onglyza dan obat-obatan lain
Komunikasikan kepada dokter atau apoteker anda apabila anda sedang, pernah, atau akan mengkonsumsi obat-obatan lain.

Secara khusus, anda harus memberitahukan dokter anda apabila anda sedang mengkonsumsi obat-obatan yang mengandung bahan aktif sebagai berikut

- Carbamazepine, phenobarbital, phenytoin. Obat-obatan ini digunakan untuk mengendalikan kejang/ayan atau nyeri kronis
- Deksametason – obat steroid. Obat ini digunakan untuk mengobati peradangan di anggota tubuh atau organ berbeda
- Rifampicin - obat antibiotik ini digunakan untuk mengobati infeksi seperti tuberculosis
- Ketokonazole – obat ini dapat digunakan untuk mengatasi infeksi jamur
- Diltiazem – obat ini digunakan untuk mengobati tekanan darah tinggi

Kehamilan dan menyusui
Bicarakan dengan dokter anda sebelum mengkonsumsi Onglyza apabila anda sedang hamil atau berencana untuk hamil. Anda sebaiknya tidak menggunakan Onglyza selama kehamilan.

Bicarakan dengan dokter anda apabila anda berencana menyusui selama mengkonsumsi Onglyza. Tidak diketahui apakah Onglyza dikeluarkan pada air susu anda. Onglyza sebaiknya tidak digunakan selama menyusui atau apabila memiliki rencana untuk menyusui.

Mengemudi dan penggunaan mesin
Apabila anda merasa pusing setelah mengkonsumsi Onglyza, jangan mengemudi atau menggunakan mesin. Hipoglikemia dapat menurunkan kemampuan anda mengemudi dan menggunakan mesin secara aman. Penggunaan Onglyza bersamaan dengan obat-obatan yang memiliki efek hipoglikemia seperti insulin atau sulfonylurea dapat meningkatkan berisiko menyebabkan hipoglikemia.

Onglyza mengandung laktosa
Tablet Onglyza mengandung laktosa (gula susu). Apabila anda dikatakan menderita intoleransi terhadap jenis gula tertentu, komunikasikan kepada dokter anda sebelum mengkonsumsi obat ini.

3. Cara menggunakan Onglyza

Selalu gunakan obat ini persis seperti yang diinstruksikan dokter anda. Apabila anda tidak yakin, periksa ulang dengan dokter, apoteker, atau perawat anda.

Dosis Onglyza yang direkomendasikan adalah satu 5 mg tablet sekali sehari.

Apabila anda menderita gangguan ginjal derajat sedang, dokter anda dapat meresepkan dosis yang lebih rendah. Dosis diberikan dalam bentuk tablet 2.5 mg sekali sehari. Untuk dosis ini, tersedia tablet dengan kekuatan berbeda.

Dokter anda dapat meresepkan Onglyza dengan kombinasi dengan insulin atau obat-obatan antidiabetik oral lainnya seperti Metformin, golongan sulfonylurea (contohnya : glibencamide, glipizide, gliclazide, gliquidone, glimepiride), dan golongan Thiazolidinedione (Pioglitazone).

Apabila memungkinkan, ingatlah untuk mengkonsumsi obat-obatan ini sesuai anjuran dokter anda untuk hasil yang maksimal demi kesehatan anda.

Cara menggunakan Onglyza
Tablet tidak boleh dipecah maupun dipotong. Telan tablet dalam keadaan utuh dengan air. Anda dapat meminum tablet ini dengan atau tanpa makanan. Tablet dapat diminum kapan saja sepanjang hari, namun demikian, usahakan untuk meminum tablet pada waktu yang sama setiap harinya. Hal ini akan memudahkan anda mengingat minum obat.

Apabila anda menggunakan Onglyza dalam jumlah lebih dari yang seharusnya
Apabila anda mengkonsumsi lebih banyak tablet Onglyza dari yang seharusnya, segera bicarakan dengan dokter anda.

Apabila anda lupa menggunakan Onglyza
- Apabila anda lupa mengkonsumsi Onglyza, minumlah segera setelah anda ingat. Meskipun demikian, apabila sudah mendekati waktu untuk minum dosis berikutnya, loncati dosis yang terlupa.
- Jangan pernah mengkonsumsi dosis ganda untuk mengganti dosis yang terlupa. Jangan pernah mengkonsumsi dua tablet dalam satu hari.

Apabila anda berhenti menggunakan Onglyza
Teruskan penggunaan Onglyza sampai dokter anda mengatakan untuk berhenti. Hal ini bertujuan untuk menjaga kadar gula darah anda.

Apabila anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan pada dokter atau apoteker anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat mengakibatkan efek samping, yang tidak dialami oleh setiap orang.

Beberapa gejala memerlukan perhatian medis segera:
Anda harus berhenti menggunakan Onglyza dan menemui dokter anda segera apabila anda mengalami gejala kadar gula darah rendah berikut ini: gemetar, berkeringat, gelisah, pandangan kabur, bibir kesemutan, pucat, perubahan suasana hati, kebingungan (hipoglikemia); terjadi cukup sering, mempengaruhi lebih dari 1 dari 10 orang.

Gejala reaksi alergi berat (jarang terjadi, mempengaruhi sampai 1 dari 1000 orang) meliputi:
- Ruam
- Bercak bentol pada kulit anda
- Pembengkakkan pada wajah, bibir, lidah, dan tenggorokan yang dapat menyebabkan kesulitan bernafas atau menelan.

Apabila anda mengalami gejala-gejala ini, hentikan penggunakan Onglyza dan hubungi dokter atau perawat anda segera. Dokter anda dapat meresepkan obat-obatan untuk mengatasi reaksi alergi dan obat lain untuk mengobati diabetes anda.

Anda harus segera menghentikan penggunaan Onglyza dan menghubungi dokter anda segera apabila anda merasakan efek samping serius sebagai berikut:
- Nyeri perut berat dan menetap yang dapat menjalar sampai ke punggung, serta mual dan muntah, hal-hal ini dapat merupakan tanda peradangan pankreas (pankreatitis).

Anda harus menghubungi dokter anda apabila anda mengalami efek samping sebagai berikut:

- Nyeri sendi hebat

Beberapa pasien dapat mengalami berikut ini ketika menggunakan Onglyza dengan metformin:

- Sering (mempengaruhi 1 sampai 10 diantara 100 pasien); infeksi rongga thoraks atas atau paru, infeksi saluran kemih, peradangan lambung atau usus yang biasa disebabkan oleh infeksi (gastroenteritis), infeksi sinus disertai sensasi penuh dan nyeri di belakang pipi dan mata (sinusitis), peradangan hidung dan tenggorokkan (nasofaringitis) (tanda-tanda penyakit ini dapat berupa masuk angin atau sakit tenggorokan), nyeri kepala, nyeri otot (myalgia), muntah, peradangan lambung (gastritis), nyeri perut, dan maag (dyspepsia).
- Jarang: nyeri sendi (arthralgia), dan kesulitan mempertahankan ereksi atau mempertahankan ereksi (disfungsi erektil).

Beberapa pasien dapat mengalami efek samping berikut ini ketika menggunakan Onglyza dengan sulfonilurea:

- Sangat sering: gula darah rendah (hipoglikemia)
- Sering: infeksi thoraks bagian atas dan paru, infeksi saluran kemih, peradangan lambung atau usus yang biasa disebabkan oleh infeksi (gastroenteritis), infeksi sinus disertai sensasi penuh dan nyeri di belakang pipi dan mata (sinusitis), nyeri kepala, nyeri perut, dan muntah.
- Jarang: kelelahan, kadar lipid yang tidak normal (dislipidemia, hipertrigliseridemia).

Beberapa Beberapa pasien dapat mengalami efek samping berikut ini ketika menggunakan Onglyza dengan thiazolidinedione:

- Sering: infeksi thoraks bagian atas dan paru, infeksi saluran kemih, peradangan lambung atau usus yang biasa disebabkan oleh infeksi (gastroenteritis), infeksi sinus disertai sensasi penuh dan nyeri di belakang pipi dan mata (sinusitis), nyeri kepala, muntah, nyeri perut, pembengkakkan tangan, pergelangan kaki atau kaki (edema perifer).

Beberapa pasien mengalami konstipasi dalam frekuensi yang tidak diketahui (frekuensi tidak dapat ditentukan dari data yang tersedia) saat menggunakan Onglyza secara tunggal maupun dengan kombinasi bersama obat lainnya.

Pelaporan efek samping
Apabila anda mengalami efek samping, hubungi dokter, apoteker, atau perawat anda. Hal ini termasuk efek samping yang mungkin terjadi yang tidak disebutkan dalam leaflet ini.

5. Cara penyimpanan Onglyza

Jauhkan obat ini dari penglihatan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah lewat tanggal kadaluwarsa yang dapat dilihat pada blister atau karton setelah tanda 'EXP'. Tanggal kadaluwarsa disini mengacu pada tanggal terakhir bulan yang tercantum.

Obat ini tidak memerlukan petunjuk penyimpanan khusus

Jangan gunakan obat ini jika kemasan dalam keadaan rusak atau adanya tanda – tanda kerusakan.

Jangan membuang obat ini pada saluran pembuangan air atau tempat sampah rumah tangga. Mintalah petunjuk dari apoteker tentang tata cara pembuangan sisa obat yang sudah tidak digunakan. Hal ini dapat membantu melindungi lingkungan hidup.

6. Isi kemasan dan informasi lain

Onglyza mengandung:

- Bahan aktif berupa saxagliptin

Setiap tablet salut selaput 2.5 mg Onglyza mengandung 2.5 mg saxagliptin (dalam bentuk hidroklorida)
Setiap tablet salut selaput 5 mg Onglyza mengandung 5 mg saxagliptin (dalam bentuk hidroklorida)

- Bahan-bahan lain berupa:

Inti Tablet: laktose monohidrate; selulosa, microcrystalline (E460i); croscarmellose sodium (E468); magnesium stearate
Bahan penyalut: polyvinyl alcohol; macrogol 3350, titanium dioxide (E171); talc (E553b) and iron oxide yellow (E172).
Tinta penanda : shellac; indigo carmine aluminium lake (E132).

Bentuk sediaan dan isi kemasan:

Onglyza 2.5 mg

- Tablet salut selaput 2.5 mg berwarna kuning pucat mengarah kuning teranng, bikonveks, dan bulat. Terdapat tulisan "2.5" tercetak pada satu sisi, dan "4214" pada sisi lainnya dalam tinta biru.
- Tablet tersedia dalam blister aluminium foil
- Tablet 2.5 mg tersedia dalam paket berukuran 14 tablet salut selaput dalam blister non perforasi.

Onglyza 5 mg

- Tablet salut selaput 5 mg berwarna merah jambu, bikonveks, dan bulat. Terdapat tulisan "5" tercetak pada satu sisi, dan "4215" pada sisi lainnya dalam tinta biru.
- Tablet tersedia dalam blister aluminium foil
- Tablet 5 mg tersedia dalam paket berukuran 14 tablet salut selaput dalam blister non perforasi.

Pemegang Hak Pemasaran dan Produsen
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