NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ONGLYZA® 2.5 mg film coated tablets
ONGLYZA® 5 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains either 2.5 mg or 5 mg saxagliptin (as hydrochloride).

Excipients: Each tablet contains 99 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

Onglyza 2.5 mg: Pale yellow to light yellow, biconvex, round, film coated tablet, with “2.5” printed on one side and “4214” printed on the other side, in blue ink.

Onglyza 5 mg: Pink, biconvex, round, film coated tablet, with “5” printed on one side and “4215” printed on the other side, in blue ink.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Add-on combination therapy
ONGLYZA is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

4.2 DOSE AND METHOD OF ADMINISTRATION

Add-on combination therapy

The recommended dose of ONGLYZA is 5 mg once daily. When ONGLYZA is used in combination with a sulphonylurea, a lower dose of sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

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

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Special populations

Elderly (≥65 years)

No dose adjustment is recommended based solely on age (see sections 4.4, 5.1 and 5.2).

Patients with renal impairment

Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter (see sections 4.4 and 5.2).

Mild renal Impairment

No dose adjustment is recommended for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2 (by Modified Diet in Renal Disease [MDRD] eGFR equation).

Moderate renal impairment

No dosage adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 m^2.

For patients with moderate renal impairment with eGFR < 45 mL/min/1.73 m^2, the dose is 2.5 mg once daily.

Severe renal impairment

For patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) requiring haemodialysis the dose is 2.5 mg once daily. ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment (see section 5.2). 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 4.4).

Paediatric and adolescent 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.

ONGLYZA tablets must not be split or cut.

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4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients, or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock and angioedema, to any dipeptidyl peptidase 4 (DPP4) inhibitor. (See sections 4.4 and 4.8)

4.4 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.

Acute Pancreatitis

Use of DPP4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis; persistent, severe abdominal pain. If pancreatitis is suspected, ONGLYZA should be discontinued; if acute pancreatitis is confirmed, ONGLYZA should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In post-marketing experience of saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis.

Renal impairment

In patients with eGFR < 45 mL/min/1.73 m^2, the dose is 2.5 mg once daily (see section 4.2). 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 sections 4.2 and 5.2).

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 4.2).

Use with medicines 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, including spontaneous reports and clinical trials, 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 4.3 and 4.8).

Geriatric use

Saxagliptin and its major metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function (see sections 4.2 and 5.1).

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). Skin lesions were not observed at an increased incidence in clinical trials. Postmarketing reports of rash have been described in the DPP4 inhibitor class. Rash is also noted as an adverse event for ONGLYZA (section 4.8). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Bullous pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP4 inhibitor use, including saxagliptin. In reported cases, patients typically responded to topical or systemic immunosuppressive treatment and discontinuation of the DPP4 inhibitor. If a patient develops blisters or erosions while receiving ONGLYZA and bullous pemphigoid is suspected, ONGLYZA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (see section 4.8).

Cardiac failure

Experience in NYHA class IV is limited. In the SAVOR trial a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established (see section 5.1). Additional analysis did not indicate a differential effect among NYHA classes. Caution is warranted if ONGLYZA is used in patients who have known risk factors for hospitalisation for heart failure, such as a history of heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms.

Arthralgia

Joint pain, which may be severe, has been reported in postmarketing reports for DPP4 inhibitors (see section 4.8). 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.

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 programme. 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 4.5).

Lactose

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

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4.5 INTERACTION WITH OTHER MEDICINES 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).

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 4.4).

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 CYP3A4/5 inducer.

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, the active components of a combined oral contraceptive (ethinyl oestradiol and norgestimate), diltiazem or ketoconazole.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The use of saxagliptin has not been studied in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. ONGLYZA should not be used during pregnancy unless clearly necessary.

Breast-feeding

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 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

When driving or using machines, it should be taken into account that dizziness has been reported with saxagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when ONGLYZA is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. sulphonylureas).

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials reported in ≥5% of patients treated with ONGLYZA 5 mg and more commonly than in patients treated with placebo are upper respiratory tract infection (7.7%), urinary tract infection (6.8%) and headache (6.5%).

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 randomised, controlled, double-blind clinical trials (including developmental and postmarketing experience), over 17,000 patients with type 2 diabetes have been treated with ONGLYZA.

In a pooled analysis of 1,681 patients with type 2 diabetes including 882 patients treated with ONGLYZA 5 mg, randomised in five double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control, 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 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 from the pooled analysis of five studies of glycaemic control, plus an additional active-controlled study of initial combination with metformin 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 from clinical trials and post marketing experience.

System organ class Adverse Reaction	Frequency of adverse reactions by treatment regimen				
	Saxagliptin monotherapy	**Saxagliptin with metformin[1]**	**Saxagliptin with a sulphonylurea (glibenclamide)**	**Saxagliptin with a thiazolidine dione**	**Saxagliptin as add-on to metformin plus a sulph-onylurea**
Infections and infestations					
Upper respiratory infection	Common	Common	Common	Common	
Urinary tract infection	Common	Common	Common	Common	
Gastroenteritis	Common	Common	Common	Common	
Sinusitis	Common	Common	Common	Common	
Nasopharyngitis		Common[2]			
Immune system disorders					
Hypersensitivity reactions†‡	Uncommon	Uncommon	Uncommon	Uncommon	
Anaphylactic reactions including anaphylactic shock†‡	Rare	Rare	Rare	Rare	
Metabolism and nutrition disorders					
Hypoglycaemia			Very common[3]		
Dislipidemia			Uncommon		
Hypertriglyceridemia			Uncommon		
Nervous system disorders					
Dizziness	Common				Common
Headache	Common	Common	Common	Common	
Gastrointestinal disorders					
Abdominal pain†	Common	Common	Common	Common	
Diarrhoea[4]	Common	Common	Common	Common	
Dyspepsia		Common			
Flatulence					Common
Gastritis		Common			
Nausea†	Common	Common	Common	Common	
Vomiting	Common	Common	Common	Common	
Pancreatitis†	Uncommon	Uncommon	Uncommon	Uncommon	

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System organ class Adverse Reaction	Frequency of adverse reactions by treatment regimen				
	Saxagliptin monotherapy	**Saxagliptin with metformin[1]**	**Saxagliptin with a sulphonylurea (glibenclamide)**	**Saxagliptin with a thiazolidine dione**	**Saxagliptin as add-on to metformin plus a sulph-onylurea**
Constipation†	Not known	Not known	Not known	Not known	Not known
Skin and subcutaneous tissue disorders					
Rash[2]	Common	Common	Common		
Dermatitis†	Uncommon	Uncommon	Uncommon	Uncommon	
Pruritus†	Uncommon	Uncommon	Uncommon	Uncommon	
Urticaria†	Uncommon	Uncommon	Uncommon	Uncommon	
Angioedema†	Rare	Rare	Rare	Rare	
Bullous pemphigoid†	Not known	Not known	Not known	Not known	Not known
Musculo-skeletal and connective tissue disorders					
Arthralgia*		Uncommon			
Myalgia[5]		Common			
Reproductive system and breast disorders					
Erectile disfunction		Uncommon			
General disorders and administration site conditions					
Fatigue	Common		Uncommon		Common
Oedema peripheral				Common	

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 diarrhoea 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).

SAVOR trial results

The SAVOR trial included 8240 patients treated with ONGLYZA 5 mg or 2.5 mg once daily and 8173 patients on placebo. Physicians were permitted to adjust other medications, including

antihyperglycaemic agents. The overall incidence of adverse events in patients treated with ONGLYZA in this trial was similar to placebo (72.5% versus 72.2%, respectively).

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.

The overall incidence of reported hypoglycaemia (recorded in daily patient diaries) was 17.1% in subjects treated with ONGLYZA and 14.8% among patients treated with placebo. The percent of subjects with reported on-treatment events of major hypoglycaemia (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 hypoglycaemia and major hypoglycaemia observed in the saxagliptin-treated group occurred primarily in subjects treated with sulphonylurea at baseline and not in subjects on insulin or metformin monotherapy at baseline. The increased risk of overall and major hypoglycaemia was primarily observed in subjects with HbA1C <7% at baseline.

Decreased lymphocyte counts were reported in 0.5% of ONGLYZA treated patients and 0.4% of placebo-treated patients.

Hospitalisation 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 favouring placebo [HR = 1.27; 95% CI 1.07, 1.51); P = 0.007]. See also section 5.1.

Description of selected adverse reactions

Hypoglycaemia

Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required.

When used as add-on combination therapy with metformin plus sulphonylurea, the overall incidence of reported hypoglycaemia was 10.1% for Onglyza 5 mg and 6.3% for placebo.

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.

Investigations

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

ONGLYZA had 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).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action and pharmacodynamic effects

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

In randomised, controlled, double-blind clinical trials (including developmental and postmarketing experience), over 17,000 patients with type 2 diabetes have been treated with saxagliptin.

<u>Glycaemic control</u>

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. 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.

<u>Saxagliptin as monotherapy</u>

Two double-blind, placebo-controlled studies of 24-week duration were conducted to evaluate the efficacy and safety of saxagliptin monotherapy in patients with type 2 diabetes.

In both studies, once-daily treatment with saxagliptin provided significant improvements in HbA1c.

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 provided significant improvements in HbA1c, FPG and PPG compared to treatment 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 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 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 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.

Saxagliptin add-on combination therapy with metformin and sulphonylurea

A total of 257 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin (5 mg once daily) in combination with metformin plus sulphonylurea in patients with inadequate glycemic control (HbA1c ≥ 7% and ≤ 10%). Saxagliptin (n=127) provided significant improvements in HbA1c and PPG compared with the placebo (n=128). The HbA1c change for saxagliptin compared to placebo was -0.7% at Week 24.

Saxagliptin add-on to dapagliflozin plus metformin therapy

A 24-week randomised, double-blind, placebo-controlled study conducted in patients with type 2 diabetes mellitus compared saxagliptin 5 mg with placebo as add-on therapy in individuals with HbA1c 7-10.5% treated with dapagliflozin (a SGLT2-inhibtor) and metformin. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks).

Individuals treated with saxagliptin added to dapagliflozin and metformin (n=153) achieved statistically significantly (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo added to dapagliflozin plus metformin (n=162) at 24 weeks (see Table 2). The effect on HbA1c observed at Week 24 was sustained at Week 52. The safety profile of saxagliptin added to dapagliflozin plus metformin in the long-term treatment period was consistent with that observed in the 24-week treatment period in this study and in the trial in which saxagliptin and dapagliflozin were given concomitantly as add-on therapy to patients treated with metformin (described below).

Proportion of patients achieving HbA1c < 7%

The proportion of patients achieving HbA1c < 7% at Week 24 was higher in the saxagliptin 5 mg plus dapagliflozin plus metformin group 35.3% (95% CI [28.2, 42.4]) compared to the placebo plus dapagliflozin plus metformin group 23.1% (95% CI [16.9, 29.3]). The effect in HbA1c observed at Week 24 was sustained at Week 52.

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

	Mean baseline HbA1c (%)	Mean change[2] from baseline HbA1c (%) at Week 24	Placebo-corrected mean change in HbA1c (%) at Week 24 (95% CI)
MONOTHERAPY STUDIES			
• Study CV181011 (n=103)	8.0	-0.5	-0.6 (-0.9, -0.4)[3]
• Study CV181038 (n=69)	7.9	-0.7 (morning)	-0.4 (-0.7, -0.1)[4]
(n=70)	7.9	-0.6 (evening)	-0.4 (-0.6, -0.1)[5]
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 D1680L00006: add-on to metformin plus SU (n=257)	8.4	-0.7	-0.7 (-0.9, -0.5)[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[6]			
Overall population (n=306)	9.4	-2.5	-0.5 (-0.7, -0.4)[7]
Baseline HbA1c ≥ 10% stratum (n=107)	10.8	-3.3	-0.6 (-0.9, -0.3)[8]
• Study CV181168: sequential add-on to dapagliflozin + metformin (n=315)	7.9	-0.5	-0.4 (-0.5, -0.2)[9]
• Study CV181057: add-on to insulin (+/-metformin)	8.7	-0.7	-0.4 (-0.6, -0.2)[3]
Overall population (n=300)			

n=Randomised 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] p=0.0059 compared to placebo.
[5] p=0.0157 compared to placebo.
[6] Metformin was uptitrated from 500 to 2000 mg per day as tolerated.
[7] Mean HbA1c change is the difference between the saxagliptin+metformin and metformin alone groups (p<0.0001).
[8] Mean HbA1c change is the difference between the saxagliptin+metformin and metformin alone groups.
[9] Mean HbA1c change is the difference between the saxagliptin+dapagliflozin+metformin and dapagliflozin+metformin groups (p< 0.0001).

Saxagliptin and dapagliflozin add-on to metformin therapy

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone (HbA1c 8%-12%), participated in this 24-week randomised, double-blind, active comparator-controlled trial to compare the combination of saxagliptin and dapagliflozin added concurrently to metformin, versus saxagliptin or dapagliflozin added to metformin. Patients were randomised to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin, saxagliptin 5 mg and placebo added to metformin, or dapagliflozin 10 mg and placebo added to metformin.

The saxagliptin and dapagliflozin group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see Table 3).

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Table 3 HbA1c at Week 24 in active-controlled study comparing the combination of saxagliptin and dapagliflozin added concurrently to metformin with either saxagliptin or dapagliflozin added to metformin

Efficacy parameter	Saxagliptin 5 mg + dapagliflozin 10 mg + metformin N=179[2]	Saxagliptin 5 mg + metformin N=176[2]	Dapagliflozin 10 mg + metformin N=179[2]
HbA1c (%) at week 24[1]			
Baseline (mean)	8.93	9.03	8.87
Change from baseline (adjusted mean[3]) (95% Confidence interval [CI])	−1.47 (−1.62, −1.31)	−0.88 (−1.03, −0.72)	−1.20 (−1.35, −1.04)
Difference from saxagliptin + metformin (adjusted mean[3]) (95% CI)	−0.59[4] (−0.81, −0.37)	-	-
Difference from dapagliflozin + metformin (adjusted mean[3]) (95% CI)	−0.27[5] (−0.48, −0.05)	-	-

[1] LRM = Longitudinal repeated measures (using values prior to rescue).
[2] Randomised and treated patients with baseline and at least 1 post baseline efficacy measurement.
[3] Least squares mean adjusted for baseline value.
[4] p-value < 0.0001.
[5] p-value=0.0166.

Proportion of patients achieving HbA1c < 7%

In the saxagliptin and dapagliflozin combination group, 41.4% (95% CI [34.5, 48.2]) of patients achieved HbA1c levels of less than 7% compared to 18.3% (95% CI [13.0, 23.5]) of patients in the saxagliptin group and 22.2% (95% CI [16.1, 28.3]) of patients in the dapagliflozin group.

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.

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Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus- Thrombolysis in Myocardial Infarction (SAVOR) Study

SAVOR was a CV outcome trial in 16,492 patients with HbA1c ≥6.5% and <12% (12,959 with established CV disease; 3533 with multiple risk factors only) who were randomised to saxagliptin (n=8,280) or placebo (n=8,212) added to regional standards of care for HbA1c and CV risk factors. The study population included those ≥65 years (n=8,561) and ≥ 75 years (n=2,330), with normal or mild renal impairment (n=13,916) as well as moderate (n=2,240) or severe (n=336) renal impairment.

The primary safety (noninferiority) and efficacy (superiority) 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 ischaemic stroke.

After a mean follow up of 2 years, the trial met its primary safety endpoint demonstrating saxagliptin does not increase the cardiovascular risk (CV death, nonfatal myocardial infarction, or nonfatal ischaemic stroke) in patients with type 2 diabetes compared to placebo when added to current background therapy (Hazard Ratio [HR] 1.00; 95% Confidence Interval: 0.89, 1.12; P=0.99 for superiority; P<0.001 for noninferiority).

The primary efficacy endpoint was not met.

Table 4: Primary and Secondary Clinical Endpoints by Treatment Group in the SAVOR Study*

Endpoint	Saxagliptin (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 noninferiority (based on HR <1.3) compared to placebo.

§ p-value = 0.99 for superiority (based on HR <1.0) compared to placebo.

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

¶ Significance not tested.

One component of the secondary composite endpoint, hospitalisation 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 (i.e. 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 hospitalisation 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.

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HbA1C was lower with saxagliptin compared to placebo in an exploratory analysis.

Elderly population

In the SAVOR study subgroups over 65 and over 75 years of age, efficacy and safety was consistent with the overall study population.

GENERATION was a 52-week glycaemic control study in 720 elderly patients, the mean age was 72.6 years; 433 subjects (60.1%) were <75 years of age, and 287 subjects (39.9%) were ≥75 years of age. Primary endpoint was the proportion of patients reaching HbA1c <7% without confirmed or severe hypoglycaemia. There appeared to be no difference in percentage responders: saxagliptin 37.9% (saxagliptin) and 38.2% (glimepiride) achieved the primary endpoint. A lower proportion of patients in the saxagliptin group (44.7%) compared to the glimepiride group (54.7%) achieved an HbA1c target of 7.0%. A lower proportion of patients in the saxagliptin group (1.1%) compared to the glimepiride group (15.3%) experienced a confirmed or severe hypoglycaemic event.

5.2 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 Cmax values were 24 ng/ml and 47 ng/ml, respectively. The intra-subject coefficients of variation for saxagliptin Cmax 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 Cmax and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach Cmax (Tmax) 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 C_{max} of saxagliptin or its major metabolite.

In subjects with CrCl > 50 mL/min (approximates to GFR $\geq$ 45 mL/min by MDRD eGFR equation), 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 these patients is not recommended. In subjects with renal impairment with CrCl $\leq$ 50 mL/min (approximates to GFR < 45 mL/min) 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. In these patients, the dose of ONGLYZA should be reduced to 2.5 mg once daily (see sections 4.2 and 4.4).

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.

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5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core:

- Lactose monohydrate
- Cellulose microcrystalline (E460i)
- Croscarmellose sodium (E468)
- Magnesium stearate

Film coating:

- Polyvinyl alcohol
- Macrogol/3350
- Titanium dioxide (E171)
- Talc (E553b)
- Iron oxide red (E172) – 5 mg only
- Iron oxide yellow (E172) – 2.5 mg only

Printing ink:

- Shellac
- Indigo carmine aluminium lake (E132)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Alu/Alu blisters containing 28 tablets or 7 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

ONGLYZA 2.5 mg: 20 September 2012
ONGLYZA 5 mg: 21 October 2010

10. DATE OF REVISION OF THE TEXT

22 October 2019
EU SPC
CDS 020919

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 & 4.8	Bullous pemphigoid is added.
8	Postal address updated.