1.5.5 PROFESSIONAL INFORMATION (PROPOSED CLEAN)

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ONGLYZA® 2,5; ONGLYZA® 5 (Film-coated Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ONGLYZA 2,5:

Each tablet contains saxagliptin hydrochloride equivalent to 2,5 mg saxagliptin free base.

ONGLYZA 5:

Each tablet contains saxagliptin hydrochloride equivalent to 5 mg saxagliptin free base.

Contains sugar: lactose monohydrate 99 mg.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablets

ONGLYZA 2,5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with “2.5” printed on one side and “4214” printed on the reverse side, in blue ink.
ONGLYZA 5 mg tablets are pink, biconvex, round, film-coated tablets with “5” printed on one side and “4215” printed on the reverse side, in blue ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Monotherapy:

ONGLYZA is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Combination therapy:

Add-on combination:

ONGLYZA is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, a thiazolidinedione, a sulfonylurea, or insulin (with or without metformin) when the single agent alone, with diet and exercise, does not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology

Monotherapy and add-on combination therapy:

The recommended dose of ONGLYZA is 5 mg once daily as monotherapy or as add-on combination therapy with metformin, a thiazolidinedione, a sulfonylurea, or insulin (with or without metformin).

Special populations

Use in the elderly:

No dosage adjustment for ONGLYZA is required based solely on age. 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.

Renal impairment:

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

Mild renal impairment:

No dosage adjustment is required 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 haemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Hepatic impairment:

No dosage adjustment for ONGLYZA is necessary for patients with mild or moderate hepatic insufficiency (see section 4.3).

Paediatric populations

Safety and effectiveness of ONGLYZA in paediatric and adolescent patients have not been established.

Method of administration

ONGLYZA can be taken with or without food

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4.3 Contraindications

ONGLYZA is contraindicated in patients with a history of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to saxagliptin or any other components of ONGLYZA, or to any other dipeptidyl peptidase-4 (DPP4) inhibitor (see section 4.4 and section 4.8).
ONGLYZA is contraindicated in patients with severe hepatic impairment.
ONGLYZA is contraindicated in patients with a previous history of pancreatitis.
ONGLYZA should not be used with type 1 diabetes or for the treatment of diabetic ketoacidosis.

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

During post-marketing experience, the following adverse reactions have been reported with use of ONGLYZA: serious hypersensitivity reactions, including anaphylaxis and angioedema. If a serious hypersensitivity reaction is suspected, discontinue ONGLYZA immediately and switch to another class of treatment for diabetes (see section 4.4 and section 4.8).

Use in patients with 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 periodically thereafter.

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 section 4.2)

Use with medications known to cause hypoglycaemia:
The sulfonylurea class of anti-hyperglycaemic agents is known to cause hypoglycaemia. Therefore, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycaemia when used in combination with ONGLYZA.

Pancreatitis:
During 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. If pancreatitis is suspected, ONGLYZA should be discontinued immediately (see section 4.3 and section 4.8).

Heart failure:
In a clinical trial, there was an increase in the rate of hospitalisation for heart failure in ONGLYZA-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 hospitalisation for heart failure, such as a history of heart failure or moderate to severe renal impairment.

Patients with a prior history of heart failure and patients with renal impairment had a higher risk for hospitalisation for heart failure. Patients should be advised of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of ONGLYZA.

Arthralgia:

During clinical trials and as reported during post-marketing experience, there have been reported adverse reactions of joint pain, which may be severe. Patients experienced relief of symptoms after discontinuation of the medication and some patients experienced recurrence of symptoms with reintroduction of ONGLYZA or another DPP4 inhibitor. Onset of symptoms following initiation of ONGLYZA may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of ONGLYZA should be individually assessed (see section 4.8).

Bullous pemphigoid:

Post-marketing 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)

ONGLYZA contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take ONGLYZA.

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 medicines 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, the pharmacokinetics of saxagliptin, its major metabolite, or the exposure to the total active components of saxagliptin (parent + metabolite) were not meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, rifampicin, omeprazole, aluminum hydroxide + magnesium hydroxide + simethicone combination, or famotidine.

In addition, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, or an oestrogen/progestin combined oral contraceptive.

4.6 Fertility, pregnancy and lactation

Safety has not been demonstrated in pregnancy and lactation.

Pregnancy

Pregnant women should not be treated with ONGLYZA. Saxagliptin crosses the placenta into the foetus following dosing in pregnant rats.

Breastfeeding

Saxagliptin is secreted in the milk of lactating rats. It is not known whether saxagliptin is secreted in human milk. Mothers receiving ONGLYZA should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No studies on the effects of ONGLYZA 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 ONGLYZA.

4.8 Undesirable effects

a. **Summary of the safety profile**

There were 4 148 patients with type 2 diabetes randomised, including 3 021 patients treated with ONGLYZA, in 6 double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of ONGLYZA on glycaemic control.

Discontinuation of therapy due to adverse events was higher in patients who received ONGLYZA 5 mg as compared to placebo (3,3 % as compared to 1,8 %).

b. **Tabulated summary of adverse reactions**

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); very rare (< 1/10 000) and not known (cannot be estimated from available data).

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 thiazolidinedione
Infections and infestations				
Upper respiratory infection	Common			
Urinary tract infection	Common			
Gastroenteritis	Common			
Sinusitis	Common			
Nasopharyngitis		Common		
Metabolism and nutrition disorders				
Hypoglycaemia			Uncommon[2]	
Nervous system disorders				
Headache	Common	Common		
Gastrointestinal disorders				
Abdominal pain	Common			
Vomiting	Common			
General disorders and administration site conditions				
Oedema peripheral[3]				Common

[1] Initial combination with metformin.

[2] 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 %).

[3]In add-on to thiazolidinedione (TZD) study, the incidence of peripheral oedema was common and higher for ONGLYZA 5 mg as compared to placebo (8,1 % as compared to 4,3 %).

Post-marketing experience:

During post-marketing experience, the following adverse reactions have been reported with use of ONGLYZA: acute pancreatitis, arthralgia, bullous pemphigoid and hypersensitivity reactions, including anaphylaxis, angioedema, rash and urticaria (see section 4.3 and section 4.4)

Toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalized exanthematous pustulosis (AGEP), erythroderma (generalized exfoliative dermatitis) have been reported in patients treated with DPP-4 inhibitors.

c. Description of selected adverse reactions

A grouping of hypersensitivity-related events in the 5-study pooled analysis up to Week 24 showed an incidence of 1,5 % and 0,4 % in patients who received ONGLYZA 5 mg and placebo, respectively.

Adverse reactions associated with ONGLYZA and concomitant therapy:

In the 2 monotherapy studies, the add-on to metformin study, and the add-on to thiazolidinedione (TZD) study, the incidence of adverse reactions of confirmed hypoglycaemia in patients treated with ONGLYZA 5 mg was similar to placebo.

In the add-on to insulin study, the overall incidence of reported hypoglycaemia was 18,4 % for ONGLYZA 5 mg and 19,9 % for placebo.

In a pooled analysis of the 2 monotherapy studies, the add-on to metformin study, and the add-on to sulfonylurea study, the overall incidence of adverse reactions of peripheral oedema observed in patients treated with ONGLYZA 5 mg was similar to placebo (1,7 % as compared to 2,4 %).

Laboratory Findings

From a baseline mean absolute lymphocyte count of approximately 2 200 cells/microL, there was a mean decrease of approximately 100 cells/microL relative to placebo in a pooled analysis of five placebo-controlled clinical studies.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects will be exacerbated and exaggerated.

Appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite are removed by haemodialysis (23 % of dose over 4 hours).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2 Oral hypoglycaemics

Saxagliptin is a selective, reversible, competitive, DPP4 (dipeptidyl peptidase-4) inhibitor. Saxagliptin demonstrates selectivity for DPP4 versus other DPP enzymes, including DPP8 and DPP9. Saxagliptin has extended binding to the DPP4 active site, prolonging its inhibition of DPP4. Saxagliptin exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of these active intact incretin hormones are increased by saxagliptin, thereby increasing and prolonging the actions of these hormones.

Incretin hormones are released by the intestine throughout the day, and concentrations are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When

blood glucose concentrations are elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

Concentrations of GLP-1 are reduced in patients with type 2 diabetes, but saxagliptin increases active GLP-1 and GIP, potentiating these mechanisms. By increasing and prolonging active incretin concentrations, saxagliptin increases insulin release and decreases glucagon concentrations in the circulation in a glucose-dependent manner.

Saxagliptin reduces fasting and postprandial glucose concentrations in patients with type 2 diabetes through effects on alpha and beta cell function as reflected by the actions described below.

Fasting glucose-dependent insulin secretion:

Saxagliptin increases pancreatic beta-cell responsiveness to glucose in the fasting state and leads to enhanced insulin secretion and glucose disposal in the presence of elevated glucose concentrations.

Postprandial glucose-dependent insulin secretion:

Saxagliptin increases pancreatic beta-cell responsiveness to glucose in the postprandial state and leads to enhanced postprandial insulin secretion and glucose disposal.

Postprandial glucagon secretion:

In type 2 diabetes, paradoxical increases in glucagon secretion from alpha cells following meals stimulate hepatic glucose production and contribute to glycaemic dysregulation. Saxagliptin moderates glucagon secretion and lowers postprandial glucagon concentrations.

General:

In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent beta cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

5.2 Pharmacokinetic properties

The pharmacokinetics of saxagliptin has been characterised in healthy subjects and patients with type 2 diabetes. Saxagliptin was absorbed after oral administration, with maximum saxagliptin plasma concentrations (C_{max}) usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in the saxagliptin dose.

Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC (INF) values for saxagliptin and its active metabolite were 78 ng·h/ml and 214 ng·h/ml, respectively. The corresponding plasma C_{max} values were 24 ng/ml and 47 ng/ml, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12 %. Following a single oral dose of 5 mg saxagliptin to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin was 2,5 hours, and the mean $t_{1/2}$ value for plasma DPP4 inhibition was 26,9 hours. The inhibition of plasma DPP4 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.

No appreciable accumulation was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2,5 mg to 400 mg. Results from population-based exposure modelling suggest that the pharmacokinetics of saxagliptin and its active metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption:

The amount of saxagliptin absorbed following an oral dose is at least 75 %. Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with a high-fat meal resulted in no change in saxagliptin C_{max} and a 27 % increase in AUC compared with the fasted state. The time for saxagliptin to reach C_{max} (T_{max}) was increased by approximately 0,5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Distribution:

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels.

Metabolism:

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

Excretion:

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24 %, 36 % and 75 % of the dose was excreted in the urine as saxagliptin, its major metabolite, and total radioactivity respectively. The average renal clearance of saxagliptin (~230 ml/min) was greater than the average estimated glomerular filtration rate (~120 ml/min), suggesting some active renal excretion. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. A total of 22 % of the administered radioactivity was recovered in faeces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed saxagliptin from the gastrointestinal tract.

Pharmacokinetics of the major metabolite:

Following oral doses of 2,5 mg to 400 mg saxagliptin in the fed or fasted states, the mean AUC values for the major metabolite range from 2- and 7-times higher than the parent saxagliptin exposures on a molar basis. Following a single oral dose of 10 mg saxagliptin in the fasted state, the mean terminal half-life ($t_{1/2}$) value for the major metabolite was 3,1 hours, and no appreciable accumulation was observed upon repeated once-daily dosing at any dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Microcrystalline cellulose

Croscarmellose sodium

Magnesium stearate

Film-coating:

Polyvinyl alcohol

Polyethylene glycol

Titanium dioxide

Talc

Iron oxide yellow (ONGLYZA 2,5 only)

Iron oxide red (ONGLYZA 5 only)

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container until required for use.

6.5 Nature and contents of container

Aluminium laminate/Aluminium foil blister strips containing multiple of 10 tablets (in a 30's pack size) packed in a cardboard carton.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals Pty Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191,

South Africa

8 REGISTRATION NUMBERS

ONGLYZA 2,5 mg tablets: 43/21.2/0608

ONGLYZA 5 mg tablets: 43/21.2/0609

9 DATE OF FIRST AUTHORISATION

ONGLYZA 2,5 mg tablets: 25 November 2011

ONGLYZA 5 mg tablets: 25 November 2011

10 DATE OF REVISION OF THE TEXT

25 November 2022