APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME (and dosage form):

Trajenta®

film-coated tablets

COMPOSITION:

Each film-coated tablet contains linagliptin 5 mg.
Inactive ingredients: copovidone, magnesium stearate, maize starch, mannitol, Opadry® pink, starch pregelatinised.
Sugar (sucrose) and lactose free.

PHARMACOLOGICAL CLASSIFICATION:

A 21.2 Oral hypoglycaemics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4, EC 3.4.14.5) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both these incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after a meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10 000 fold selectivity versus DPP-8 or DPP-9 activity *in vitro*.

Pharmacokinetics:

The pharmacokinetics of linagliptin has been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was well absorbed, with peak plasma concentrations (median Tmax) occurring 1,5 hours post dose.

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life, more than 100 hours. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. After once daily dosing, steady state plasma concentrations of 5 mg linagliptin are reached by the third dose. Plasma AUC of linagliptin increased approximately 33 % following 5 mg doses at steady state compared to the first dose. The

intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12,6 % and 28,5 %, respectively). Plasma AUC of linagliptin increased in a less than dose-proportional manner. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption:
The absolute bioavailability of linagliptin after oral administration is approximately 30 %. Because co-administration of a high fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food. *In vitro* studies indicated that linagliptin is a substrate of P-glycoprotein and of CYP3A4. Ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, led to a twofold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin, a potent inducer of P-gp and CYP3A, resulted in an about 40 % decreased linagliptin steady-state AUC, presumably by increasing/decreasing the bioavailability of linagliptin by inhibition/induction of P-glycoprotein.

Distribution:
As a result of tissue binding, the mean apparent volume of distribution at steady state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1 110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99 % at 1 nmol/L to 75 – 89 % at $\geq$ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70 – 80 % of linagliptin was bound to other plasma proteins than DPP-4, hence 30 – 20 % were unbound in plasma.

Metabolism:
Following a [^{14}C] linagliptin oral 10 mg dose, approximately 5 % of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13,3 % of linagliptin at steady state was detected which was found to be pharmacologically inactive and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Excretion:
Following administration of an oral [^{14}C] linagliptin dose to healthy subjects, approximately 85 % of the administered radioactivity was eliminated in faeces (80 %) or urine (5 %) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Special Populations:
Renal Insufficiency:
A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to < 80 mL/min), moderate (30 to < 50 mL/min), and severe (< 30 mL/min), as well as patients with end stage renal disease (ESRD) on haemodialysis. In addition, patients with type 2 diabetes

mellitus (T2DM) and severe renal impairment (< 30 mL/min) were compared to T2DM patients with normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:
CrCl = [140 – age] x weight (kg) x 0,85 (if female)/serum creatinine (µmol/L).

Under steady state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1,7 fold was observed compared with control. Exposure in T2DM patients with severe renal impairment (RI) was increased by about 1,4 fold compared to T2DM patients with normal renal function. Steady state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of renal insufficiency. In addition, mild renal insufficiency had no effect on linagliptin pharmacokinetics in patients with type 2 diabetes as assessed by population pharmacokinetic analyses.

Hepatic Insufficiency:
In patients with mild, moderate and severe hepatic insufficiency (according to the Child-Pugh classification), mean AUC and Cmax of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin. No dosage adjustment for linagliptin is necessary for patients with mild, moderate or severe hepatic insufficiency.

Body Mass Index (BMI):
No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Geriatric:
No dosage adjustment is required based on age, as age did not have a clinically relevant impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric:
Studies characterising the pharmacokinetics of linagliptin in paediatric patients have not been yet performed.

INDICATIONS:
TRAJENTA is indicated in adult patients with type 2 diabetes mellitus (T2DM) to improve glycaemic control in conjunction with diet and exercise, as monotherapy or as add-on to metformin, sulphonylureas, thiazolidinediones, insulin (with or without metformin and/or pioglitazone and/or sulphonylurea) or metformin plus sulphonylureas.

CONTRA-INDICATIONS:
Hypersensitivity to linagliptin or any of the excipients of TRAJENTA.
Pancreatitis or history of pancreatitis (see **WARNINGS**).

WARNINGS AND SPECIAL PRECAUTIONS:
General:
TRAJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis:
There have been post-marketing reports of acute pancreatitis in patients taking TRAJENTA. If pancreatitis is suspected, TRAJENTA should be discontinued (see **CONTRA-INDICATIONS)**.

Hypoglycaemia:
TRAJENTA alone showed a comparable incidence of hypoglycaemia to placebo.
In clinical trials of TRAJENTA as part of combination therapy with agents not known to cause hypoglycaemia (metformin, thiazolidinediones) rates of hypoglycaemia reported with TRAJENTA were similar to rates in patients taking placebo.
Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when TRAJENTA is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered.

Bullous pemphigoid:
Bullous pemphigoid has been observed in patients taking linagliptin. If bullous pemphigoid is suspected, TRAJENTA should be discontinued.

Rhabdomyolysis:
Rhabdomyolysis has been reported during use of DPP-4 inhibitor containing products such as TRAJENTA. However, causality could not be assessed due to confounding factors such as concomitant use of medicines (statins, colchicine, etc.) or co-morbid conditions (renal failure, hypovolemia, etc.), known to cause or predispose to development of rhabdomyolysis. Close monitoring of patients using DPP-4 inhibitor containing products in presence of predisposing risk factors is recommended.

Effects on ability to drive and use machines:
No studies on the effects on the ability to drive and use machines have been performed.

INTERACTIONS:
In vitro assessment of medicine interactions:
Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4 but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.
Linagliptin is a P-glycoprotein substrate and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* medicine interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

In vivo assessment of medicine interactions:
Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low. No clinically significant interactions requiring dose adjustment were observed. Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin or oral contraceptives providing *in vivo* evidence of a low propensity for causing medicine interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Metformin:
Co-administration of multiple three-times-daily doses of 850 mg metformin with a supratherapeutic dose of 10 mg linagliptin once daily did not clinically meaningfully alter the pharmacokinetics of linagliptin or metformin in healthy volunteers. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulphonylureas:
The steady-state pharmacokinetics of 5 mg linagliptin were not changed by co-administration of a single 1,75 mg dose glibenclamide (glyburide) and multiple oral doses of 5 mg linagliptin. However, there was a clinically not relevant reduction of 14 % of both AUC and Cmax of glibenclamide. Because glibenclamide is primarily metabolised by CYP2C9, these data also support the conclusion that linagliptin is not a CYP2C9 inhibitor. Clinically meaningful interactions would not be expected with other sulphonylureas (e.g. glipizide, tolbutamide and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Thiazolidinediones:
Co-administration of multiple daily doses of 10 mg linagliptin (supratherapeutic) with multiple daily doses of 45 mg pioglitazone, a CYP2C8 and CYP3A4 substrate, had no clinically relevant effect on the pharmacokinetics of either linagliptin or pioglitazone or the active metabolites of pioglitazone, indicating that linagliptin is not an inhibitor of CYP2C8-mediated metabolism *in vivo* and supporting the conclusion that the *in vivo* inhibition of CYP3A4 by linagliptin is negligible.

Ritonavir:
A study was conducted to assess the effect of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, on the pharmacokinetics of linagliptin. Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir increased the AUC and Cmax of linagliptin approximately twofold and threefold, respectively. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will not be associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors and dose adjustment is not required.

Rifampicin:
A study was conducted to assess the effect of rifampicin, a potent inductor of P-glycoprotein and CYP3A4, on the pharmacokinetics of 5 mg linagliptin. Multiple co-

administration of linagliptin with rifampicin, resulted in a 39,6 % and 43,8 % decreased linagliptin steady-state AUC and Cmax and about 30 % decreased DPP-4 inhibition at trough. Thus, linagliptin in combination with strong P-gp inducers is expected to be clinically efficacious, although full efficacy might not be achieved.

Digoxin:
Co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0,25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy volunteers. Therefore, linagliptin is not an inhibitor of P-glycoprotein-mediated transport *in vivo*.

Warfarin:
Multiple daily doses of 5 mg linagliptin did not alter the pharmacokinetics of S(-) or R(+) warfarin, a CYP2C9 substrate, showing that linagliptin is not an inhibitor of CYP2C9.

Simvastatin:
Multiple daily doses of 10 mg linagliptin (supratherapeutic) had a minimal effect on the steady-state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy volunteers. Following administration of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34 %, and the plasma Cmax by 10 %. Therefore, linagliptin is considered to be a weak inhibitor of CYP3A4-mediated metabolism, and dosage adjustment of concomitantly administered substances metabolised by CYP3A4 is considered unnecessary.

Oral Contraceptives:
Co-administration with 5 mg linagliptin did not alter the steady-state pharmacokinetics of levonorgestrel or ethinylestradiol.

The absolute bioavailability of linagliptin is approximately 30 %.
Because co-administration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food.

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has not been established.

Pregnancy:
TRAJENTA should not be used during pregnancy.

Lactation:
Available pharmacodynamic/toxicological data in animals have shown excretion of linagliptin/metabolites in milk.
It is not known whether this medicine is excreted in human milk.
TRAJENTA should not be used in women breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE:
Adults:
The recommended dose is 5 mg once daily. TRAJENTA can be taken with or without a meal at any time of the day.

Renal impairment:
No dose adjustment is required for patients with renal impairment.

Hepatic Impairment:
No dose adjustment is required for patients with hepatic impairment.

Elderly:
No dose adjustment is necessary.

Children and adolescents:
TRAJENTA is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

Missed dose:
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.

SIDE EFFECTS:
The safety of TRAJENTA has been evaluated overall in 6 602 patients with T2DM of which 5 955 patients received the target dose of 5 mg.

In placebo-controlled studies, 6 666 patients were included and 4 302 patients were treated with the therapeutic dose of 5 mg linagliptin. 3 964 patients were exposed to linagliptin 5 mg once daily for $\geq$ 12 weeks.

In the pooled analysis of the placebo-controlled trials, the overall incidence of AEs in patients treated with placebo was similar to linagliptin 5 mg (63,1 % versus 60,3 %). Discontinuation of therapy due to AEs was higher in patients who received placebo as compared to linagliptin 5 mg (4,4 % versus 3,3 %).

Due to the impact of the background therapy on adverse events (e.g. on hypoglycaemias), adverse events were analysed and displayed based on the respective treatment regimens (monotherapy, add-on to metformin, add-on to thiazolidinedione (PPARγ agent)), add-on to sulphonylurea, and add-on to metformin plus sulphonylurea, and add-on to insulin.

The placebo-controlled studies included 18 studies where linagliptin was given either as
- monotherapy with short-term duration of up to 4 weeks
- monotherapy with $\geq$ 12 week duration
- add-on to metformin
- initial combination therapy with pioglitazone
- add-on to sulphonylurea
- add-on to metformin + sulphonylurea
- add-on to insulin (with or without metformin and/or pioglitazone and/or sulphonylurea).

Adverse reactions classified by system organ class (SOC) and MedDRA preferred terms reported in patients who received 5 mg TRAJENTA in the 18 double-blind studies as monotherapy, initial combination therapy or as add-on therapy are presented per treatment regimen in the table below (see table 1).

Table 1. Adverse reactions reported in patients who received TRAJENTA 5 mg daily as monotherapy or as add-on therapies (pooled analysis of placebo-controlled studies):

Frequency classes: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000).
Not known (cannot be estimated from available data).

	Adverse reactions by treatment regimen					
SOC	**Linagliptin (monotherapy)**	**Linagliptin + Metformin**	**Linagliptin + Sulphonylurea**	**Linagliptin + Pioglitazone**	**Linagliptin + Insulin**	**Linagliptin + Metformin + Sulphonylurea**
Infections & infestations	Uncommon: nasopharyngitis	Uncommon: nasopharyngitis	Not known: nasopharyngitis	Not known: nasopharyngitis	Uncommon: nasopharyngitis	Not known: nasopharyngitis
Immune system disorders	Not Known: hypersensitivity	Rare: hypersensitivity	Not known: hypersensitivity	Not known: hypersensitivity	Not known: hypersensitivity	Not known: hypersensitivity
Metabolism & nutrition disorders						Very common: hypoglycaemia
			Not known: hyper-triglyceridaemia			
				Not known: hyperlipidaemia		
Respiratory, thoracic & mediastinal disorders	Uncommon: cough	Uncommon: cough	Not known: cough	Not known: cough	Uncommon: cough	Not known: cough
Gastrointestinal disorders	Not known: pancreatitis	Not known: pancreatitis	Not known: pancreatitis	Not known: pancreatitis	Uncommon: pancreatitis	Not known: pancreatitis
					Uncommon: constipation	
Investigations				Common: weight increased		

The most frequently reported adverse event was hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea 22,9 % vs. 14,8 % in placebo.
Hypoglycaemias in the placebo-controlled studies (10,9 %; N = 471) were mild (80 %; N = 384) or moderate (16,6 %; N = 78) or severe (1,9 %; N = 9).

Side effects identified from post-marketing experience:
From post-marketing experience the following side effects have been reported:

SOC	Adverse reaction
Immune system disorders	angio-oedema
	urticaria

Skin and subcutaneous tissue disorders	bullous pemphigoid
	severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), erythema multiforme and erythroderma (generalised exfoliative dermatitis)
Musculoskeletal and connective tissue disorders	rhabdomyolysis

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

During controlled clinical trials in healthy subjects, single doses of up to 600 mg TRAJENTA (equivalent to 120 times the recommended dose) were well tolerated. There is no experience with doses above 600 mg in humans.

Treatment:

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required.

IDENTIFICATION:

Light red, round, biconvex, bevel-edged, film-coated tablets, one side debossed with BI company symbol, the other side debossed with 'D5'.

PRESENTATION:

Aluminium foil blister packs of 30 tablets. Printed cardboard cartons contain 3 blister cards of 10 tablets each.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

45/21.2/0557

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Ingelheim Pharmaceuticals (Pty) Ltd
Pine Avenue
Randburg
South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of Registration: 15 August 2013
Revised: 18 January 2022

NAMIBIA Reg. No. 12/21.2/0268	NS2

BOTSWANA Reg. No. BOT1302425	S2

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