AUSTRALIAN PRODUCT INFORMATION – TRAJENTA (linagliptin) film-coated tablet

1 NAME OF THE MEDICINE

linagliptin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRAJENTA are film-coated tablets for oral administration containing 5 mg linagliptin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

TRAJENTA tablets are round, light red, biconvex, bevel-edged film-coated tablets, one side debossed with the Boehringer Ingelheim company logo and on the other side debossed with 'D5'. Each tablet contains 5 mg linagliptin.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRAJENTA is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise,

as monotherapy when metformin and sulfonylureas are not tolerated, or are contraindicated, or

as add on to metformin, sulfonylureas or metformin plus sulfonylureas, or to insulin (with or without metformin) or

as add on to metformin plus SGLT2 inhibitors.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults: The recommended dose is 5 mg once daily.

TRAJENTA 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.

The elderly: No dose adjustment is necessary.

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

Patients with renal impairment: No dosage adjustment is required for patients with renal impairment.

Patients with hepatic impairment: No dosage adjustment is required for patients with hepatic impairment.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active ingredient or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

TRAJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis

Acute pancreatitis has been observed in patients taking linagliptin. If pancreatitis is suspected, TRAJENTA should be discontinued.

Hypoglycaemia

Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.

In clinical trials of linagliptin as part of combination therapy with agents not known to cause hypoglycaemia (metformin), rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo.

Sulfonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulfonylurea and/or insulin. A dose reduction of the sulfonylurea or insulin may be considered.

Bullous pemphigoid

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

Arthralgia

There have been postmarketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with linagliptin.

Combination with glucagon like peptide (GLP-1) analogues

Linagliptin has not been studied in combination with glucagon like peptide 1 (GLP-1) analogues.

Use in the elderly

See Section 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special patient groups.

Paediatric use

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

Effects on laboratory tests

See Section 4.8 Adverse Effects (Undesirable Effects), Laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic Interactions

In vitro assessment of drug 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 inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on this result and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-glycoprotein substrates. However, as linagliptin is a P-glycoprotein substrate, inhibitors/inducers of this transporter may affect linagliptin plasma kinetics.

In vivo assessment of drug 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 drug 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 clinical meaningfully alter the

pharmacokinetics of linagliptin or metformin in healthy volunteers. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulfonylureas: The steady-state pharmacokinetics of 5 mg linagliptin were not changed by co-administration 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 sulfonylureas (e.g. glipizide, tolbutamide and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

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 two-fold and three-fold, 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 or 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-glycoprotein inducers is expected to be clinically efficacious, although full efficacy might not be achieved.

Digoxin: Co-administration of multiple 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No studies on the effect on human fertility have been conducted for TRAJENTA. No adverse effects on fertility were observed in male and female rats given linagliptin orally up to the highest dose of 240 mg/kg/day (yielding approximately 1000 times the plasma AUC obtained in patients at the maximum recommended human dose [MRHD] of 5 mg/day prior to and throughout mating.

Use in Pregnancy (Category B3)

There are limited data from the use of linagliptin in pregnant women. Linagliptin was shown to cross the placenta in rats and rabbits.

In animal embryofetal development studies, linagliptin was shown to be not teratogenic in rats at oral doses up to 240 mg/kg/day (approximately 1000 times the exposure in patients at the MRHD, based on plasma AUC) and up to 150 mg/kg/day in the rabbit (approximately 2000 times human exposure). However, postimplantation loss was increased in both species at these upper dose levels (together with maternotoxicity), and there was an increase in runts and a slight increase in the incidence of

fetal visceral variations in the rabbit. No adverse effects on embryofetal development were observed at up to 30 mg/kg/day in the rat (50 times human exposure) and up to 25 mg/kg/day in the rabbit (78 times human exposure). However, as animal studies are not always predictive of human response, as a precautionary measure, it is preferable to avoid the use of TRAJENTA during pregnancy.

Use in Lactation

Linagliptin and its metabolites were shown to be readily excreted in the milk of lactating rats. A risk to the newborns / infants cannot be excluded. TRAJENTA should not be used during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effect on the ability to drive and use machines have been performed. If patients experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Adverse Events in Clinical Trials

The safety of TRAJENTA has been evaluated overall in 11,341 patients with type 2 diabetes mellitus of which 10,694 patients received the target dose of 5 mg.

In placebo-controlled studies, 10,963 patients were included and 6,580 patients were treated with the therapeutic dose of 5 mg linagliptin. 6,061 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 adverse events in patients treated with placebo was similar to linagliptin 5 mg (63.4% versus 59.1%). Discontinuation of therapy due to adverse events was higher in patients who received placebo as compared to linagliptin 5 mg (4.3% versus 3.4%).

Due to the impact of the background therapy on adverse events (e.g. on hypoglycaemias), adverse events were analysed based on the respective treatment regimens (monotherapy, add on to metformin, add on to sulfonylurea, add on to metformin plus sulfonylurea, add on to insulin, and add on to metformin and SGLT2 inhibitors).

TRAJENTA 5 mg once daily was studied as monotherapy in two placebo-controlled trials of 18- and 24 weeks duration. Seven placebo-controlled studies investigated linagliptin in combination with other anti-glycaemic agents: two with metformin (12- and 24-weeks treatment duration); one with a sulfonylurea (18-weeks treatment duration); one with metformin and sulfonylurea (24-week treatment duration); one with insulin (primary endpoint at 24 weeks); and one with metformin and empagliflozin (24-weeks). In placebo-controlled clinical studies, adverse reactions that occurred in $\geq$ 5% of patients receiving TRAJENTA (n = 2566) and more commonly than in patients given placebo (n = 1183) included nasopharyngitis (5.8% vs 5.5%).

Adverse reactions reported in ≥ 2% of patients treated with TRAJENTA 5 mg daily as monotherapy or in combination with sulfonylurea, metformin, insulin or metformin plus an SGLT2 inhibitor and at least 2-fold more commonly than in patients treated with placebo are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥ 2% of Patients Treated with TRAJENTA and at Least 2-Fold Greater than with Placebo in Placebo-Controlled Clinical Studies of TRAJENTA Monotherapy or Combination Therapy

	Linagliptin + Metformin # n (%)		Linagliptin + Sulfonylurea n (%)		Linagliptin + Metformin + Sulfonylurea n (%)		Linagliptin + Insulin n (%)		Linagliptin (Monotherapy)* n (%)		Linagliptin + Metformin + SGLT2 inhibitor n (%)	
SOC Adverse reaction	**TRAJENTA n = 590**	**Placebo n = 248**	**TRAJENTA n = 161**	**Placebo n = 84**	**TRAJENTA n = 791**	**Placebo n = 263**	**TRAJENTA n = 631**	**Placebo n = 630**	**TRAJENTA n = 765**	**Placebo n = 458**	**TRAJENTA n = 236**	**Placebo n = 240**
Infections & infestations												
Nasopharyngitis	--	--	7 (4.3)	1 (1.2)	--	--	--	--	--	--	--	--
Metabolism & nutrition disorders												
Hypertriglyceridaemia†	--	--	4 (2.4)	0 (0.0)	--	--	--	--	--	--	--	--
Respiratory, thoracic & mediastinal disorders												
Cough	--	--	--	--	19 (2.4)	3 (1.1)	--	--	--	--	--	--

* Pooled data from 7 studies
\# Pooled data from 2 studies
† Includes reports of hypertriglyceridemia (n = 2; 1.2%) and blood triglycerides increased (n = 2; 1.2%)

In addition to the adverse reactions specified in Table 1, 'lipase increased' also represents an adverse reaction that was reported in ≥ 2% of patients treated with TRAJENTA and at least 2-fold greater than with placebo in a placebo-controlled clinical trial. Lipase increases above 3 times the upper limit of normal was observed in 1.7% in placebo group and 8.2% in the TRAJENTA group in Study 1218.89.

Following 52 weeks treatment in a controlled study comparing linagliptin with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥ 5% patients treated with linagliptin (n = 776) and more frequently than in patients treated with a sulfonylurea (n = 775) were arthralgia (5.7% vs 3.5%), back pain (6.4% vs 5.2%), and headache (5.7% vs 4.2%).

Other adverse reactions reported in clinical studies with treatment of TRAJENTA were hypersensitivity (e.g., urticaria, angioedema, localised skin exfoliation, or bronchial hyperreactivity), myalgia and amylase increased. Urinary tract infections have also been reported at a higher rate in patients treated with TRAJENTA in combination with sulfonylurea compared to patients treated with placebo (3.1% vs 0.0%).

Other adverse reactions reported in clinical studies with treatment of TRAJENTA + insulin are listed below by system organ class and frequency according to the following categories: Very common ≥ 10%, Common ≥ 1% and < 10%, Uncommon ≥ 0.1% and < 1%, Rare ≥ 0.01% and < 0.1%, Very rare < 0.01%, Not known:

System Organ Class Adverse reaction	Linagliptin
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity	uncommon
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon
Gastrointestinal disorders	
Constipation	uncommon
Pancreatitis	uncommon

In the clinical trial program, pancreatitis was reported in 8 of 4687 patients (4311 patient years of exposure) while being treated with TRAJENTA compared with 0 of 1183 patients (433 patient years of exposure) treated with placebo. Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycaemia

In the placebo-controlled studies, 195 (7.6%) of the total 2566 patients treated with TRAJENTA 5 mg reported hypoglycaemia compared to 49 patients (4.1%) of 1183 placebo treated patients. The incidence of hypoglycaemia was similar to placebo when linagliptin was administered as monotherapy or in combination with metformin or with pioglitazone. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 of 791 (22.9%) of patients reported hypoglycaemia compared with 39 of 263 (14.8%) of patients administered placebo in combination with metformin and a sulfonylurea.

In the 24-week study of patients receiving TRAJENTA as add-on therapy to insulin, no significant difference in the incidence of hypoglycaemia was noted between the TRAJENTA (25.5%) and insulin only (26.3%) treated groups.

Laboratory Tests

Changes in laboratory findings were similar in patients treated with TRAJENTA 5 mg compared to patients treated with placebo. Changes in laboratory values that occurred more frequently in the TRAJENTA group and ≥ 1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the TRAJENTA group).

In the CAROLINA study comparing linagliptin with active comparator glimepiride (see Section 5.1 Pharmacodynamic Properties, Clinical Trials) laboratory analysis of amylase showed increases to > 3xULN in 0.99% of patients treated with linagliptin and in 0.54% of patients treated with glimepiride.

Postmarketing Experience

From postmarketing experience, the following adverse reactions have been reported and are listed below by system organ class and frequency according to the following categories:

Common ≥ 1% and < 10%, Uncommon ≥ 0.1% and < 1%, Rare ≥ 0.01% and < 0.1%, Very rare (< 0.01%), not known (cannot be estimated from the available data).

System Organ Class Adverse reaction	Linagliptin
Immune system disorders	
Angioedema	rare
Urticaria	rare

System Organ Class Adverse reaction	**Linagliptin**
Skin and subcutaneous tissue disorders	
Rash	uncommon
Bullous pemphigoid	not known*
Gastrointestinal disorders	
Mouth ulceration	rare
Musculoskeletal and connective tissue disorders	
Arthralgia	rare
Myalgia	rare
Rhabdomyolysis	rare

*See also Linagliptin cardiovascular and renal safety study (CARMELINA) below

Linagliptin cardiovascular and renal safety study (CARMELINA)

The CARMELINA study evaluated the cardiovascular and renal safety of linagliptin versus placebo in patients with type 2 diabetes and with increased CV risk evidenced by a history of established macrovascular or renal disease (see section 5.1 Pharmacodynamic Properties, Clinical trials). The study included 3,494 patients treated with linagliptin (5 mg) and 3,485 patients treated with placebo. Both treatments were added to standard of care targeting regional standards for HbA1c and CV risk factors. At baseline, 57 % of patients were treated with insulin, 54 % with metformin, and 32 % with a sulfonylurea. The overall incidence of adverse events and serious adverse events in patients receiving linagliptin was similar to that in patients receiving placebo. Safety data from this study was in line with previous known safety profile of linagliptin.

In the treated population, severe hypoglycaemic events (requiring assistance) were reported in 3.0% of patients on linagliptin and in 3.1% on placebo. Among patients who were using sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.0% in linagliptin-treated patients and 1.7% in placebo treated patients. Among patients who were using insulin at baseline, the incidence of severe hypoglycaemia was 4.4% in linagliptin-treated patients and 4.9% in placebo treated patients.

In the overall study observation period adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo.

In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients treated with linagliptin and in no patient treated with placebo.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: DPP-4 inhibitor, ATC code: A10BH05

Mechanism of action

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4), 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 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 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 binding to DPP-4 is reversible but long lasting and thus leads to a sustained increase and a prolongation of active incretin levels. *In vitro*, linagliptin inhibits DPP-4 with nanomolar potency and exhibits a >10000 fold selectivity versus DPP-8 or DPP-9 activity.

Clinical trials

Eight phase III randomised controlled trials involving 5,239 patients with type 2 diabetes, of which 3,319 were treated with linagliptin were conducted to evaluate efficacy and safety. These studies had 929 patients of 65 years and over who were on linagliptin. There were also 1,238 patients with mild renal impairment, and 143 patients with moderate renal impairment on linagliptin. Linagliptin once daily produced clinically significant improvements in glycaemic control, with no clinically relevant change in body weight. Reductions in HbA1c were seen across different subgroups including gender, age, race, renal impairment and body mass index (BMI), with a higher baseline HbA1c being associated with a greater reduction in HbA1c.

<u>Linagliptin monotherapy for patients ineligible for metformin</u>

The efficacy and safety of linagliptin monotherapy was evaluated in patients for whom metformin therapy is inappropriate, due to intolerability or contraindication, in a double blind placebo controlled study of 18 weeks duration, followed by a 34 week safety extension period (placebo patients switched to glimepiride). Linagliptin (n=147), when compared to placebo (n=73), provided significant improvements in HbA1c, (-0.60% change; 95% confidence interval (-0.88, -0.32); p<0.0001), from a mean baseline HbA1c of 8.09%. The mean HbA1c change from baseline remained constant for linagliptin from week 18 to week 52. Linagliptin also showed significant improvements in fasting plasma glucose (FPG), and a greater portion of patients achieved a target HbA1c of < 7.0%, compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo and was lower than seen with glimepiride during the safety extension. Body weight did not differ significantly between the groups during the placebo controlled 18 weeks, and patients treated with glimepiride had an increase in body weight during the safety extension.

<u>Linagliptin as add on to metformin therapy</u>

The efficacy and safety of linagliptin in combination with metformin was evaluated in a double blind placebo-controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA1c (-0.64% change compared to placebo) from a mean baseline HbA1c of 8%. Linagliptin also showed significant improvements in FPG, 2-hour post-prandial glucose (PPG) and a greater portion of patients achieved a target HbA1c of < 7.0%, compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo. Body weight did not differ significantly between the groups.

The efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in combination with metformin in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo controlled study of 12 weeks duration. Linagliptin (2.5 mg twice daily and 5 mg once daily) added to metformin provided significant improvements in glycaemic parameters compared with placebo. Linagliptin 5 mg once daily and 2.5 mg twice daily provided comparable

significant HbA1c reductions of -0.80% (95% CI -1.02,-0.58; p<0.0001) (from baseline 7.98%), and -0.74% (95% CI-0.97, -0.52; p<0.0001) (from baseline 7.96%) compared to placebo.

The efficacy and safety of linagliptin in combination with metformin was evaluated in a 24-week placebo-controlled factorial study of initial therapy. Linagliptin 2.5 mg twice daily in combination with metformin (500 mg or 1000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy (mean baseline HbA1c 8.65%). The mean treatment difference in HbA1c between linagliptin+metformin combination therapy versus metformin monotherapy from baseline to Week 24 (LOCF) was -0.51% (95% CI -0.73, -0.30; p<0.0001) for linagliptin 2.5 mg+metformin 1000 mg twice daily compared to metformin 1000 mg twice daily, -0.58% (95% CI -0.79, -0.36; p<0.0001) for linagliptin 2.5 mg+metformin 500 mg twice daily compared to metformin 500 mg twice daily. The placebo-corrected mean HbA1c change from baseline for linagliptin 2.5/metformin 1000 mg twice daily was -1.71% which led to HbA1c control (<7.0%) in 53.6% of patients (compared to 30.7% on monotherapy with metformin 1000 mg twice daily). Mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values.

Linagliptin as add on to sulfonylurea therapy

The efficacy and safety of linagliptin in combination with sulphonylurea was evaluated in a double blind placebo-controlled study of 18 weeks duration. Linagliptin provided significant improvements in HbA1c (-0.47% change compared to placebo) from a mean baseline HbA1c of 8.6%. Linagliptin also showed significant improvements in patients achieving a target HbA1c of < 7.0%. Body weight did not differ significantly between the groups.

Linagliptin as add on to insulin therapy

The efficacy and safety of the addition of linagliptin 5 mg to insulin alone or in combination with metformin has been evaluated in a double blind placebo controlled study over 24 weeks duration. The mean treatment difference in HbA1c between linagliptin (n=617) versus placebo (n=618) from baseline to Week 24 (LOCF) was -0.65% (95% CI -0.74, -0.55; p<0.0001) from a mean baseline HbA1c of 8.3%. Mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values. The mean HbA1c change from baseline was sustained for linagliptin from week 12 to week 24. Linagliptin also showed significant improvements in FPG of -0.62 mmol/L (95% CI-0.90, -0.35; p<0.0001) compared to placebo, and a greater portion of patients achieved a target HbA1c of < 7.0%, compared to placebo. This was achieved with a stable insulin dose. After 24 weeks of treatment, the mean daily insulin dose at baseline was 42 units in patients treated with linagliptin and 40 units in placebo-treated patients. The mean change from baseline to Week 24 in daily dose of insulin was 1.3 IU in the placebo group and 0.6 IU in the linagliptin group. Body weight did not differ significantly between the groups. Effects on plasma lipids were neutral. The incidence of hypoglycaemia was similar across treatment groups (25.5% linagliptin; 26.3% placebo).

Linagliptin as add on to a combination of metformin and sulfonylurea therapy

A placebo controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg to placebo in patients not sufficiently treated with a combination with metformin and a sulfonylurea. Linagliptin provided significant improvements in HbA1c (-0.62% change compared to placebo) from a mean baseline HbA1c of 8.14%. Linagliptin also showed significant improvements in patients achieving a target HbA1c of < 7.0%, and also for FPG, and 2-hour PPG, compared to placebo. Body weight did not differ significantly between the groups.

Linagliptin as add-on to a combination of metformin and empagliflozin

In patients inadequately controlled with metformin and empagliflozin (10 mg (n=247) or 25 mg (n=217)), 24-weeks treatment with add-on therapy of linagliptin 5 mg provided adjusted mean HbA1c reductions from baseline by -0.53% (significant difference to add-on placebo -0.32% (95% CI -0.25, -0.13) and -0.58% (significant difference to add-on placebo -0.47% (95% CI -0.66; -0.28), respectively. A statistically significant greater proportion of patients with a baseline HbA1c ≥7.0% and treated with linagliptin 5 mg achieved a target HbA1c of <7% compared to placebo.

In prespecified subgroups of patients with baseline HbA1c greater or equal than 8.5% (n=66 and n=42 patients on metformin plus empagliflozin 10 mg or 25 mg, respectively), the adjusted mean HbA1c reductions from baseline to 24 weeks on add-on therapy with linagliptin 5 mg were -0.97%

(p=0.0875, for difference to add-on placebo) and -1.16% (p=0.0046, for difference to add-on placebo), respectively.

Linagliptin 24 month data, as add onto metformin in comparison with glimepiride

In a study comparing the efficacy and safety of the addition of linagliptin 5 mg or glimepiride (a sulfonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy, both linagliptin and glimepiride reduced HbA1c from baseline (-0.4% for linagliptin, -0.6% for glimepiride) from a baseline mean of 7.7% after 104 weeks of treatment. In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, showed a statistically significant improvement with linagliptin compared with glimepiride treatment. The incidence of hypoglycaemia in the linagliptin group (7.5%) was significantly lower than that in the glimepiride group (36.1%). Patients treated with linagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glimepiride (-1.39 versus +1.29 kg).

Linagliptin as add on therapy in patients with severe renal impairment, 12 week placebo controlled data (stable background) and 40 week placebo controlled extension (adjustable background)

The efficacy and safety of linagliptin was also evaluated in type 2 diabetes patients with severe renal impairment in a double blind study versus placebo for 12 weeks duration, during which background glycaemic therapies were kept stable. Patients were on a variety on background therapies including insulin, sulfonylurea, glinides and pioglitazone. There was a follow up 40 week period during which dose adjustments in antidiabetes background therapies were allowed.

Linagliptin (n=52) when compared to placebo (n=52), provided significant improvements in HbA1c (-0.59% change 95% CI -0.88. -0.29; p=0.0001), from a mean baseline HbA1c of 8.2%. A greater portion of patients achieved a target HbA1c of < 7.0%, compared to placebo. The observed difference in HbA1c over placebo was -0.72% after 52 weeks.

Body weight did not differ significantly between the groups. The observed incidence of hypoglycaemia in patients treated with linagliptin was higher than placebo, due to an increase in asymptomatic hypoglycaemic events. This can be attributed to the antidiabetes background therapies (insulin and sulfonylurea or glinides). There was no difference between groups in severe hypoglycaemic events.

Linagliptin as add on therapy in elderly patients (age ≥ 70 years) with type 2 diabetes

The efficacy and safety of linagliptin in elderly (age ≥ 70 years) type 2 diabetes patients has been evaluated in a double blind study versus placebo for 24 weeks duration. Patients received metformin and/or sulfonylurea and/or insulin as background therapy. Doses of background antidiabetic medications were kept stable during the first 12 week, after which adjustments were permitted. Linagliptin (n=126) provided significant improvements in HbA1c of -0.64% (95% CI -0.81, -0.48; p<0.0001) compared to placebo (n=118) after 24 weeks, from a mean baseline HbA1c of 7.8%. Overall, HbA1c levels below 7% were achieved at 24 weeks by 39% of linagliptin subjects compared with 8% of those taking placebo (adjusted odds ratio, 8.319 (p<0.0001). A reduction in HbA1c from baseline of at least 0.5% was achieved by 54% of linagliptin versus 13% of placebo subjects. This differential response was maintained in subjects with higher baseline HbA1c levels. Linagliptin also showed significant improvements in FPG of -1.1 mmol/L (95% CI -1.7, -0.6; p<0.0001) compared to placebo. Body weight did not differ significantly between the groups. Hypoglycaemia rates were also comparable on a background of insulin with or without metformin (13 of 35 patients, 37.1% treated with linagliptin and 6 of 15 patients, 40.0% treated with placebo). However, on a background of sulfonylurea with or without metformin, hypoglycaemia was reported in a higher proportion of patients treated with linagliptin (24 of 82 patients, 29.3%) compared to placebo (7 of 42 patients, 16.7%). There was no difference between groups in severe hypoglycaemic events.

Linagliptin cardiovascular and renal safety study (CARMELINA)

CARMELINA was a randomised study in 6,979 patients with type 2 diabetes with increased CV risk evidenced by a history of established macrovascular or renal disease who were treated with linagliptin 5 mg (3,494) or placebo (3,485) added to standard of care targeting regional standards for HbA1c, CV risk factors and renal disease. The study population included 1,211 (17.4%) patients ≥75 years of age and 4,348 (62.3%) patients with renal impairment. Approximately 19% of the population

had eGFR ≥45 to <60 mL/min/1.73 m^2, 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m^2 and 15% had eGFR < 30 mL/min/1.73 m^2.

The mean HbA1c at baseline was 8.0%.

The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE). The renal composite endpoint was defined as renal death or sustained end stage renal disease or sustained decrease of 40% or more in eGFR.

The median follow-up was for 2.2 years. When added to the standard of care, linagliptin was shown to be non-inferior to placebo with regard to the risk of occurrence of the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (Table 2 and Figure 1).

For the key secondary renal endpoint, which was time to the first occurrence of renal death, sustained end stage renal disease (ESRD), or sustained decrease of 40% or more in eGFR from baseline, linagliptin was not superior to placebo (HR: 1.04; 95% CI: 0.89, 1.22) (Table 2).

The risk of the composite endpoints hospitalisation for heart failure or cardiovascular death, and hospitalisation for heart failure and all-cause mortality was also balanced across the treatment groups (Table 3).

Table 2 Major adverse cardiovascular events (MACE) and renal outcome events by treatment group in the CARMELINA study

	Linagliptin 5mg		Placebo		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
Number of patients	3,494		3,485		
Primary CV composite (Cardiovascular death, non-fatal MI, non-fatal stroke)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)**
Secondary renal composite (renal death, ESRD, 40% sustained decrease in eGFR)	327 (9.4)	48.9	306 (8.8)	46.6	1.04 (0.89, 1.22)

* PY=patient years

** Test on non-inferiority to demonstrate that the upper bound of the 95% CI for the hazard ratio is less than 1.3

Figure 1 Time to first occurrence of 3P-MACE in CARMELINA

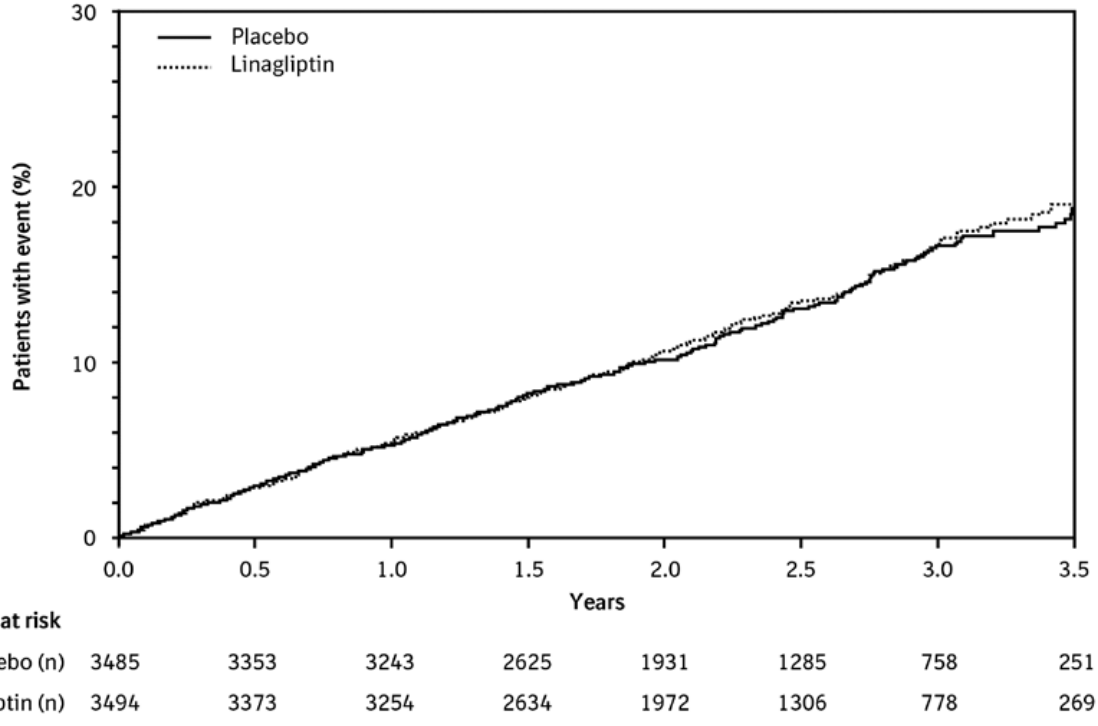


Table 3 Hospitalisation for heart failure and mortality by treatment group in the CARMELINA study

	Linagliptin 5mg		Placebo		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
Number of patients	3,494		3,485		
All-cause mortality	367 (10.5)	46.9	373 (10.7)	48.0	0.98 (0.84, 1.13)
CV death	255 (7.3)	32.6	264 (7.6)	34	0.96 (0.81, 1.14)
Hospitalisation for heart failure	209 (6.0)	27.7	226 (6.5)	30.4	0.90 (0.74, 1.08)

* PY=patient years

Linagliptin cardiovascular safety study (CAROLINA)

CAROLINA was a randomised study in 6033 patients with early type 2 diabetes and increased CV risk or established complications who were treated with linagliptin 5 mg (3023) or glimepiride 1–4 mg (3010) added to standard of care (including background therapy with metformin in 83% of patients) targeting regional standards for HbA1c and CV risk factors. The mean age for study population was 64 years and included 2030 (34%) patients ≥ 70 years of age. The study population included 2089 (35%) patients with cardiovascular disease and 1130 (19%) patients with renal impairment with an eGFR < 60mL/min/1.73m^2 at baseline. The mean HbA1c at baseline was 7.15%.

The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE).

After a median follow up of 6.25 years, linagliptin did not increase the risk of major adverse cardiovascular events (Table 4) as compared to glimepiride. Results were consistent for patients treated with or without metformin.

Table 4 Major adverse cardiovascular events (MACE) and mortality by treatment group in the CAROLINA study

	Linagliptin 5 mg		Glimepiride (1-4 mg)		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1000 PY*	Number of Subjects (%)	Incidence Rate per 1000 PY*	(95% CI)
Number of patients	3023		3010		
Primary CV composite (Cardiovascular death, non-fatal MI, non-fatal stroke)	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)**

* PY=patient years

** Test on non-inferiority to demonstrate that the upper bound of the 95% CI for the hazard ratio is less than 1.3

For the entire treatment period (median time on treatment 5.9 years) the rate of patients with moderate or severe hypoglycaemia was 6.5% on linagliptin versus 30.9% on glimepiride, severe hypoglycaemia occurred in 0.3% of patients on linagliptin versus 2.2% on glimepiride.

5.2 PHARMACOKINETIC PROPERTIES

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 volunteer patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the drug. 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 area under the curve (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 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 two-fold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin, a potent inducer of P-glycoprotein and CYP3A, resulted in an approximate 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 1110 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 ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At the peak plasma concentration in humans at 5 mg/day, approximately 10% of linagliptin is unbound.

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 and 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.

Pharmacokinetics in special patient groups:

Pharmacokinetics in children: Studies characterising the pharmacokinetics of linagliptin in paediatric patients have not been performed.

Pharmacokinetics in the elderly: 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 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

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.

Gender: No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Race: No dosage adjustment is necessary based on race. Race had no obvious effect on the plasma concentrations of linagliptin based on a composite analysis of available pharmacokinetic data, including patients of Caucasian, Hispanic, African-American, and Asian origin. In addition the pharmacokinetic characteristics of linagliptin were found to be similar in dedicated phase I studies in Japanese, Chinese and Caucasian healthy volunteers and African American type 2 diabetes patients.

Pharmacokinetics in patients with renal impairment: 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 impairment compared to normal healthy control subjects. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to < 80 mL/min), moderate (30 to < 50 mL/min), and severe (< 30 mL/min), as well as patients with end stage renal disease (ESRD) on haemodialysis. In addition, patients with type 2 diabetes mellitus and severe renal impairment (< 30 mL/min) were compared to patients with type 2 diabetes mellitus and 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 (years)] x weight (kg) {x 0.85 for female patients} / [72 x serum creatinine (mg/dL)]. 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 patients with type 2 diabetes mellitus and severe renal impairment was increased by about 1.4 fold compared to patients with type 2 diabetes mellitus and 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 impairment. In addition, mild renal impairment had no effect on linagliptin pharmacokinetics in patients with type 2 diabetes mellitus as assessed by population pharmacokinetic analyses.

Pharmacokinetics in patients with hepatic impairment: In patients with mild, moderate and severe hepatic impairment (according to the Child-Pugh classification), mean AUC and C_{max} 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 impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay in the rat.

Carcinogenicity

No evidence of carcinogenicity was observed with linagliptin in 2-year studies in mice and rats given oral doses up to 80 mg/kg/day and 60 mg/kg/day, respectively.

These doses correspond to approximately 300- and 400-times the human exposure (plasma AUC) at the MRHD of 5 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each TRAJENTA tablet contains pregelatinised maize starch, maize starch, mannitol, copovidone, magnesium stearate and the colouring agent Opadry Pink 02F34337.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

TRAJENTA is available in blister packs containing 10 (sample) and 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol and very slightly soluble in acetone. Dissociation Constants: $pKa_1 = 8.6$; $pKa_2 = 1.9$. Partition Co-efficient: Log P = 1.7 (free base); Log D (pH 7.4) = 0.4.

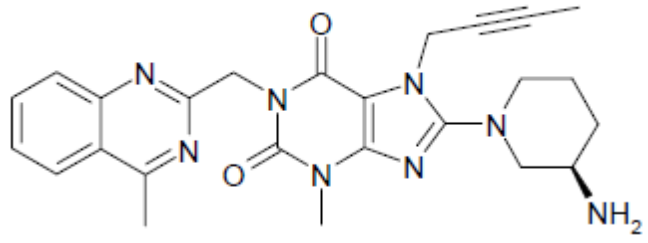
Chemical structure

Chemical name: 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

Molecular formula: $C_{25}H_{28}N_8O_2$

Molecular weight: 472.54

Structural formula:



CAS number

668270-12-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Boehringer Ingelheim Pty Limited
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9 DATE OF FIRST APPROVAL

1 November 2011

10 DATE OF REVISION

18 August 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Update to Laboratory test subsection
5.1	CAROLINA clinical trial data added