HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADJENTA safely and effectively. See full prescribing information for TRADJENTA.

Tradjenta® (linagliptin) tablets
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------

Indications and Usage	
Important Limitations of Use (1.2)	6/2013
Contraindications (4)	x/201x
Warnings and Precautions	
Pancreatitis (5.1)	6/2013
Hypersensitivity Reactions (5.3)	x/201x

----------INDICATIONS AND USAGE----------

TRADJENTA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1.1)

Important limitations of use:
- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (1.2)
- Has not been studied in patients with a history of pancreatitis (1.2)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dose of TRADJENTA is 5 mg once daily. (2.1)
- TRADJENTA can be taken with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 5 mg (3)

----------CONTRAINDICATIONS----------

History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity (4)

----------WARNINGS AND PRECAUTIONS----------
- There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis. If pancreatitis is suspected, promptly discontinue TRADJENTA. (5.1)
- When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (5.2)
- There have been postmarketing reports of serious hypersensitivity reactions in patients treated with TRADJENTA including anaphylaxis, angioedema, and exfoliative skin conditions. In such cases, promptly discontinue TRADJENTA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.3)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA or any other antidiabetic drug (5.4)

----------ADVERSE REACTIONS----------
- Adverse reactions reported in ≥5% of patients treated with TRADJENTA and more commonly than in patients treated with placebo included nasopharyngitis (6.1)
- Hypoglycemia was more commonly reported in patients treated with the combination of TRADJENTA and sulfonylurea compared with those treated with the combination of placebo and sulfonylurea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Strong P-glycoprotein/CYP3A4 inducer: The efficacy of TRADJENTA may be reduced when administered in combination (e.g., with rifampin). Use of alternative treatments is strongly recommended. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: There are no adequate and well-controlled studies in pregnant women. TRADJENTA tablets should be used during pregnancy only if clearly needed. (8.1)
- Nursing mothers: Caution should be exercised when TRADJENTA is administered to a nursing woman (8.3)
- Pediatric patients: Safety and effectiveness of TRADJENTA in patients below the age of 18 have not been established (8.4)
- Renal or hepatic impairment: No dose adjustment recommended (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: x/201x

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

TRADJENTA tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14.1)]*.

1.2 Important Limitations of Use

TRADJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

TRADJENTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using TRADJENTA *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of TRADJENTA is 5 mg once daily.

TRADJENTA tablets can be taken with or without food.

2.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When TRADJENTA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

TRADJENTA (linagliptin) 5 mg tablets are light red, round, biconvex, bevel-edged, film-coated tablets with “D5” debossed on one side and the Boehringer Ingelheim logo debossed on the other side.

4 CONTRAINDICATIONS

TRADJENTA is contraindicated in patients with a history of a hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking TRADJENTA. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue TRADJENTA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using TRADJENTA.

5.2 Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues and insulin are known to cause hypoglycemia. The use of TRADJENTA in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial *[see Adverse Reactions (6.1)]*. The use of TRADJENTA in combination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with TRADJENTA.

5.3 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with TRADJENTA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with TRADJENTA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue TRADJENTA, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with TRADJENTA.

5.4 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA tablets or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of TRADJENTA 5 mg once daily in patients with type 2 diabetes is based on 14 placebo-controlled trials, 1 active-controlled study, and one study in patients with severe renal impairment. In the 14 placebo-controlled studies, a total of 3625 patients were randomized and treated with TRADJENTA 5 mg daily and 2176 with placebo. The mean exposure in patients treated with TRADJENTA across studies was 29.6 weeks. The maximum follow-up was 78 weeks.

TRADJENTA 5 mg once daily was studied as monotherapy in three placebo-controlled trials of 18 and 24 weeks’ duration and in five additional placebo-controlled studies lasting ≤18 weeks. The use of TRADJENTA in combination with other antihyperglycemic agents was studied in six placebo-controlled trials: two with metformin (12 and 24 weeks’ treatment duration); one with a sulfonylurea (18 weeks’ treatment duration); one with metformin and sulfonylurea (24 weeks’ treatment duration); one with pioglitazone (24 weeks’ treatment duration); and one with insulin (primary endpoint at 24 weeks).

In a pooled dataset of 14 placebo-controlled clinical trials, adverse reactions that occurred in ≥2% of patients receiving TRADJENTA (n = 3625) and more commonly than in patients given placebo (n = 2176), are shown in Table 1. The overall incidence of adverse events with TRADJENTA were similar to placebo.

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

	Number (%) of Patients	
	TRADJENTA 5 mg n = 3625	**Placebo n = 2176**
Nasopharyngitis	254 (7.0)	132 (6.1)
Diarrhea	119 (3.3)	65 (3.0)
Cough	76 (2.1)	30 (1.4)

Rates for other adverse reactions for TRADJENTA 5 mg vs placebo when TRADJENTA was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when TRADJENTA was used as add-on to sulfonylurea; hyperlipidemia (2.7% vs 0.8%) and weight increased (2.3% vs 0.8%) when TRADJENTA was used as add-on to pioglitazone; and constipation (2.1% vs 1%) when TRADJENTA was used as add-on to basal insulin therapy.

Following 104 weeks' treatment in a controlled study comparing TRADJENTA with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥5% of patients treated with TRADJENTA (n = 776) and more frequently than in patients treated with a sulfonylurea (n = 775) were back pain (9.1% vs 8.4%), arthralgia (8.1% vs 6.1%), upper respiratory tract infection (8.0% vs 7.6%), headache (6.4% vs 5.2%), cough (6.1% vs 4.9%), and pain in extremity (5.3% vs 3.9%).

Other adverse reactions reported in clinical studies with treatment of TRADJENTA were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity), and myalgia. In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with TRADJENTA compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycemia
In the placebo-controlled studies, 199 (6.6%) of the total 2994 patients treated with TRADJENTA 5 mg reported hypoglycemia compared to 56 patients (3.6%) of 1546 placebo-treated patients. The incidence of hypoglycemia was similar to placebo when TRADJENTA was administered as monotherapy or in combination with metformin, or with pioglitazone. When TRADJENTA was administered in combination with metformin and a sulfonylurea, 181 of 792 (22.9%) patients reported hypoglycemia compared with 39 of 263 (14.8%) patients administered placebo in combination with metformin and a sulfonylurea. Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

In the study of patients receiving TRADJENTA as add-on therapy to a stable dose of insulin for up to 52 weeks (n=1261), no significant difference in the incidence of investigator reported hypoglycemia, defined as all symptomatic or asymptomatic episodes with a self measured blood glucose ≤70 mg/dL, was noted between the TRADJENTA- (31.4%) and placebo- (32.9%) treated groups. During the same time period, severe hypoglycemic events, defined as requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions, were reported in 11 (1.7%) of TRADJENTA treated patients and 7 (1.1%) of placebo treated patients. Events that were considered life-threatening or required hospitalization were reported in 3 (0.5%) patients on TRADJENTA and 1 (0.2%) on placebo.

Use in Renal Impairment
TRADJENTA was compared to placebo as add-on to pre-existing antidiabetic therapy over 52 weeks in 133 patients with severe renal impairment (estimated GFR <30 mL/min). For the initial 12 weeks of the study, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dose adjustments in antidiabetic background therapy were allowed.

In general, the incidence of adverse events including severe hypoglycemia was similar to those reported in other TRADJENTA trials. The observed incidence of hypoglycemia was higher (TRADJENTA, 63% compared to placebo, 49%) due to an increase in asymptomatic hypoglycemic events especially during the first 12 weeks when background glycemic therapies were kept stable. Ten TRADJENTA-treated patients (15%) and 11 placebo-treated patients (17%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying finger stick glucose ≤54 mg/dL). During the same time period, severe hypoglycemic events, defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions, were reported in 3 (4.4%) TRADJENTA-treated patients and 3 (4.6%) placebo-treated patients. Events that were considered life-threatening or required hospitalization were reported in 2 (2.9%) patients on TRADJENTA and 1 (1.5%) patient on placebo.

Renal function as measured by mean eGFR and creatinine clearance did not change over 52 weeks' treatment compared to placebo.

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

No clinically meaningful changes in vital signs were observed in patients treated with TRADJENTA.

6.2 Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of TRADJENTA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Acute pancreatitis, including fatal pancreatitis *[see Indications and Usage (1.2) and Warnings and Precautions (5.1)]*
- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions *[see Warnings and Precautions (5.3)]*
- Rash

7 DRUG INTERACTIONS

7.1 Inducers of P-glycoprotein or CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of TRADJENTA may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Linagliptin administered during the period of organogenesis was not teratogenic at doses up to 30 mg/kg in the rat and 150 mg/kg in the rabbit, or approximately 49 and 1943 times the clinical dose based on AUC exposure. Doses of linagliptin causing maternal toxicity in the rat and the rabbit also caused developmental delays in skeletal ossification and slightly increased embryofetal loss in the rat (1000 times the clinical dose) and increased fetal resorptions and visceral and skeletal variations in the rabbit (1943 times the clinical dose).

Linagliptin administered to female rats from gestation day 6 to lactation day 21 resulted in decreased body weight and delays in physical and behavioral development in male and female offspring at maternally toxic doses (exposures >1000 times the clinical dose). No functional, behavioral, or reproductive toxicity was observed in offspring of rats exposed to 49 times the clinical dose.

Linagliptin crossed the placenta into the fetus following oral dosing in pregnant rats and rabbits.

8.3 Nursing Mothers

Available animal data have shown excretion of linagliptin in milk at a milk-to-plasma ratio of 4:1. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADJENTA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of TRADJENTA in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of TRADJENTA; 1085 (27%) were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of an overdose with TRADJENTA, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

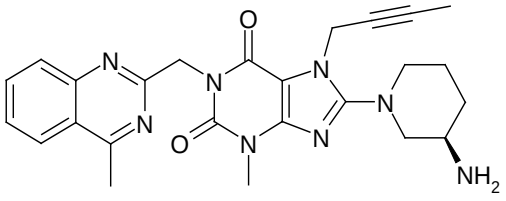
During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of TRADJENTA (equivalent to 120 times the recommended daily dose) there were no dose-related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

11 DESCRIPTION

TRADJENTA (linagliptin) tablets contain, as the active ingredient, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Linagliptin is described chemically as 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]-

The empirical formula is $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.54 g/mol. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol (<1 mg/mL), and very slightly soluble in acetone (ca. 1 mg/mL).

Each film-coated tablet of TRADJENTA contains 5 mg of linagliptin free base and the following inactive ingredients: mannitol, pregelatinized starch, corn starch, copovidone, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and red ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones 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.

12.2 Pharmacodynamics

Linagliptin binds to DPP-4 in a reversible manner and thus increases the concentrations of incretin hormones. Linagliptin glucose dependently increases insulin secretion and lowers glucagon secretion, thus resulting in better regulation of glucose homeostasis. Linagliptin binds selectively to DPP-4, and selectively inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

12.3 Pharmacokinetics

The pharmacokinetics of linagliptin has been characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a single 5-mg dose to healthy subjects, peak plasma concentrations of linagliptin occurred at approximately 1.5 hours post dose (T_{max}); the mean plasma area under the curve (AUC) was 139 nmol*h/L and maximum concentration (C_{max}) was 8.9 nmol/L.

Plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. The prolonged elimination phase 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 linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady state compared with 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 in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of linagliptin is approximately 30%. High-fat meal reduced C_{max} by 15% and increased AUC by 4%; this effect is not clinically relevant. TRADJENTA may be administered with or without food.

Distribution

The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, 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 high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metabolism

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Excretion

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

Specific Populations

Renal Impairment

An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes mellitus and severe renal impairment (CrCl <30 mL/min), and 11 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.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects.

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function.

Patients with type 2 diabetes mellitus and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes mellitus and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

These findings were further supported by the results of population pharmacokinetic analyses.

Hepatic Impairment

In patients with mild hepatic impairment (Child-Pugh class A), steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in

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