APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by Andrei Perlloni

3. acting in the capacity of Branch Chief, Drug Imports and Exports Compliance Branch

4. bears the seal/stamp of U.S. Department of Health and Human Services

Certified

5. at Washington, D.C.

6. the fifth of July, 2018

7. by *Assistant Authentication Officer, United States Department of State*

8. No. 18046402-3

9. Seal/Stamp:

10. Signature:

Chana M Turner

United States Food and Drug Administration

Center for Drug Evaluation and Research

10903 New Hampshire Ave, Silver Spring, MD 20993, United States of America

CDERExportCertificateProgram@fda.hhs.gov - Telephone (301) 796-4950

Certificate of a Pharmaceutical Product - Approved Drug Product

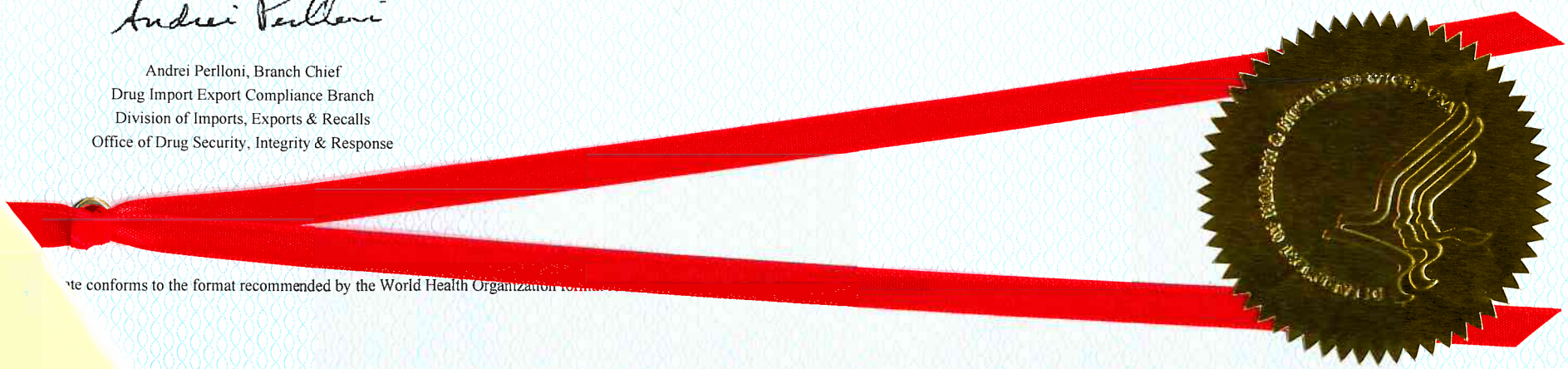
Certificate Number: **6JP6-W69P** Certificate Issue Date: **May 29, 2018** Certificate Expiration Date: **May 28, 2020**

Importing Country: **COLOMBIA** Exporting Country: **UNITED STATES of AMERICA**

1.	Drug Trade Name, International or National non-proprietary name (as applicable) & dosage form: **TRADJENTA®, Tablet**
1.1	Active Ingredient(s) and amount(s) per unit dose (complete quantitative composition is preferred): **linagliptin 5 MG**
1.2	Is this product licensed to be placed on the market for use in the exporting country? **Yes**
1.3	Is this product actually on the market in the exporting country? **Yes**
2.A.1	Product license number & date of issue: **201280 05/02/2011**
2.A.2	Product license holder name & address: **Boehringer-Ingelheim Inc., 900 Ridgebury Road, Ridgefield, CT 06877 United States of America**
2.A.3	Status of Product license holder: **Neither**
2.A.3.1	Manufacturer name & address: **West-Ward Columbus Inc., 1809 Wilson Road, Columbus, OH 43228 United States of America**
2.A.4	Is a summary basis for approval appended? **Yes**
2.A.5	Is the attached product information, complete and consonant with the license? **Yes**
2.A.6	Applicant name & address for certificate (if different from the license holder): **Boehringer-Ingelheim Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 United States of America**
2.B.4	Remarks: **API Manufacturer: Boehringer Ingelheim Pharma GmbH and Co. KG, Binger Strasse 173, Ingelheim am Rhein, Rheinland-Pfalz 55216 GERMANY** **International Trade Name: Tradjenta; Local Trade Name: Trayenta**
3.	Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? **Yes**
3.1	Periodicity of routine inspections (years): **Pursuant to section 510(h)(3) of the Federal Food, Drug & Cosmetic Act, Inspections will occur in accordance with a risk-based schedule**
3.2	Has the manufacture of this type of dosage form been inspected? **Yes**
3.3	Do the facilities and operations conform to GMPs as recommended by the WHO? (GMPs including 21 Code of Federal Regulations parts 210, 211, or ICH Q7A): **Yes, at time of inspection, site complies with FDA cGMP**
3.4	Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? **Yes**

Andrei Perlloni

Andrei Perlloni, Branch Chief
Drug Import Export Compliance Branch
Division of Imports, Exports & Recalls
Office of Drug Security, Integrity & Response



te conforms to the format recommended by the World Health Organization

D00147301



6JP6-W69P

PRODUCT AND BLISTER LABEL FOR: TRADJENTA 5 MG

Each tablet contains 5 mg of linagliptin.
Dosage: Take one tablet daily. See package insert for full dosage information.
Store at 25°C (77°F) (see insert).
Keep out of reach of children.
Dist. by: Boehringer Ingelheim (BI) Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
Mkd. by: BI Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
and
Eli Lilly and Company
Indianapolis, IN 46285 USA
Made in Germany
© 2017 BI Int'l GmbH
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L5249E

NDC 0597-0140-90 90 tablets

DISPENSE THE ACCOMPANYING MEDICATION GUIDE TO EACH PATIENT

Tradjenta®
(linagliptin) **Tablets**
5 mg

℞ only

Boehringer Ingelheim

Lilly

N 0597-0140-90

10007263/05

Tradjenta®
(linagliptin) **Tablets**
5 mg
Store at 25°C (77°F) (see insert).

N (01)103 0597-0140-61 7

Boehringer Ingelheim

Lilly

Lot
Exp.

Tradjenta®
(linagliptin) **Tablets**
5 mg
Store at 25°C (77°F) (see insert).

N (01)103 0597-0140-61 7

Boehringer Ingelheim

Lilly

Lot
Exp.

Tradjenta®
(linagliptin) **Tablets**
5 mg
Store at 25°C (77°F) (see insert).

N (01)103 0597-0140-61 7

Boehringer Ingelheim

Lilly

Lot
Exp.

TA/329/BIP/1

Tradjenta®
(linagliptin) **Tablets**
5 mg
Store at 25°C (77°F) (see insert).

N (01)103 0597-0140-61 7

Boehringer Ingelheim

Lilly

Lot
Exp.

6JP6-W69P

CARTON LABEL FOR: TRADJENTA 5 MG



AND HANDLING
INFORMATION

from the full prescribing information are not

6JP6-W69P

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, for oral use
Initial U.S. Approval: 2011

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

Warnings and Precautions	
Heart Failure (5.2)	8/2017
Bullous Pemphigoid (5.6)	12/2016

----------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)
- Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of TRADJENTA in patients who have known risk factors for heart failure. Monitor for signs and symptoms. (5.2)
- 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 (5.3)
- 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. (5.4)
- Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.5)
- There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue TRADJENTA. (5.6)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA (5.7)

----------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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2017

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- 1.2 Important Limitations of Use

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

TRADJENTA is 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 (5.4) 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 Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of TRADJENTA prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of TRADJENTA.

5.3 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.

5.4 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.

5.5 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.6 Bullous Pemphigoid

Cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving TRADJENTA. If pemphigoid is suspected, TRADJENTA should be discontinued and referral to a dermatologist should be considered for diagnosis and

defined as requiring ...
...ENTA treated patients and 7 (1.1%) o1
...%) patients on TRADJENTA and 1 (0.2%) on
...h severe renal impairment (estimated GFR <30
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...DJENTA trials. The observed inciden
...ycemic events especially during th
...o-treated patients (17%) report
...time period, severe hypoglyc
...ive actions, were reported
...r required hospitalizatior

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA tablets.

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

Pemphigoid

cases of bullous pemphigoid requir
immunosuppressive treatment
pemphigoid is suspected,

5.5 Severe and Disabling Arthralgia

There have been postmarketing reports of seve
therapy varied from one day to years. Patients e
ymptoms when restarting the same drug or a di
ppropriate.

also been reported with oth
nor because it is unknown whether such

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.

Increase in Uric Acid: 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).

Increase in Lipase: In a placebo-controlled clinical trial with TRADJENTA in type 2 diabetes mellitus patients with micro- or macroalbuminuria, a mean increase of 30% in lipase concentrations from baseline to 24 weeks was observed in the TRADJENTA arm compared to a mean decrease of 2% in the placebo arm. Lipase levels above 3 times upper limit of normal were seen in 8.2% compared to 1.7% patients in the TRADJENTA and placebo arms, respectively.

Vital Signs
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 (5.4)]*
- Severe and disabling arthralgia *[see Warnings and Precautions (5.5)]*
- Bullous pemphigoid *[see Warnings and Precautions (5.6)]*
- Rash
- Mouth ulceration, stomatitis

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
Risk Summary
The limited data with TRADJENTA use in pregnant women are not sufficient to inform of drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal reproduction studies, no adverse developmental effects were observed when linagliptin was administered to pregnant rats during the period of organogenesis at doses similar to the maximum recommended clinical dose, based on exposure *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c>7 and has been reported to be as high as 20-25% in women with HbA1c>10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data
Animal Data
No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg and 150 mg/kg, respectively. These doses represent approximately 943 times (rats) and 1943 times (rabbits) the 5 mg clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49 times the 5 mg clinical dose, based on exposure.

8.2 Lactation
Risk Summary
There is no information regarding the presence of linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADJENTA and any potential adverse effects on the breastfed child from TRADJENTA or from the underlying maternal condition.

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

Geriatric Use
Of 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 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 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.

...ded for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

...d to the saturable binding of linagliptin to ...accumulation of linagliptin, as determined ...-state plasma concentrations of linagliptin 5 ...ose. The intra-subject and inter-subject ...creased in a less than dose-proportional manner ...pe 2 diabetes.

...C by 4%, this effect is not clinically ... ...althy subjects is approxim... ...decreasing from about ... ...liptin. At high conce...

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

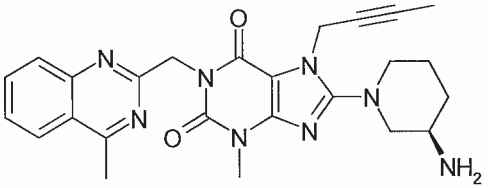
10 OVERDOSAGE
In the event of an overdose with TRADJENTA, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. 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 re[illegible] 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 approximat[illegible] that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about o[illegible] 1 nmol/L to 75%-89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concer[illegible]

[illegible] present in rat milk. Therefore, the development [illegible] any potential adverse effects on the breastfed ch[illegible]

8.4 Pediatric Use
Safety and effectiveness of TRADJENTA in ped[illegible]

eriatric Use
[illegible]e 4040 type 2 diabetes patients treated w[illegible]rs and over. Of these patients, 2566 w[illegible] No overall differences in safety or [illegible]mended in the elderly populatio[illegible]sitivity of some older individual[illegible]

[illegible]ded for patients wit[illegible]

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 terms of AUC_{0-24} and approximately 23% lower C_{max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Body Mass Index (BMI)/Weight
No dose adjustment is necessary based on BMI/weight. BMI/weight had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Gender
No dose adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Geriatric
Age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Pediatric
Studies characterizing the pharmacokinetics of linagliptin in pediatric patients have not yet been performed.

Race
No dose adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of linagliptin based on available pharmacokinetic data, including subjects of White, Hispanic, Black, and Asian racial groups.

Drug Interactions
In vitro Assessment of Drug Interactions
Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions
Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. For patients requiring use of such drugs, an alternative to linagliptin is strongly recommended. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT). No dose adjustment of TRADJENTA is recommended based on results of the described pharmacokinetic studies.

Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0

The highest dose in a 2-year study, a chromosomal aberration test in human lymphocytes, and a micronucleus test in mice in a 2-year study. Higher doses of linagliptin in female rats were associated with an increased incidence of uterine tumors in mice in a 2-year study. The highest dose young up to the highest dose of 240 mg/kg/day, which is approximately 1,100 times the maximum recommended human dose of 5 mg/day based on body surface area measure. Higher doses of linagliptin in female rats were associated with an increased incidence of uterine tumors in mice in a 2-year study. The highest dose

double-blind, placebo-controlled studies was 69% White, 29% Black, and 2% Asian, with a mean age of 57 years (range 18 to 85 years). Patients who had inadequate glycemic control on insulin.

			AUC†	Cmax
No dosing adjustments required for TRADJENTA when given with the following coadministered drugs:				
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg#	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg#	2.01	2.96
The efficacy of TRADJENTA may be reduced when administered in combination with strong inducers of CYP3A4 or P-gp (e.g., rifampin). Use of alternative treatments is strongly recommended *[see Drug Interactions (7.1)]*.				
Rifampin	600 mg QD	5 mg QD	0.60	0.56

*Multiple dose (steady state) unless otherwise noted
#Single dose
†AUC = AUC(0 to 24 hours) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
QD = once daily
BID = twice daily
TID = three times daily

Table 3 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0		
				AUC†	Cmax
No dosing adjustments required for the following coadministered drugs:					
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg#	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg#	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93** 1.03**	1.00 1.01 1.04** 1.15**
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

*Multiple dose (steady state) unless otherwise noted
#Single dose
†AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
**AUC=AUC(0-168) and C_{max}=E_{max} for pharmacodynamic end points
INR = International Normalized Ratio
PT = Prothrombin Time
QD = once daily
TID = three times daily

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.

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 fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943-times the clinical dose based on AUC exposure).

14 CLINICAL STUDIES

TRADJENTA has been studied as monotherapy and in combination with metformin, glimepiride, pioglitazone, and insulin.

A total of 3648 patients with type 2 diabetes were randomized and exposed to linagliptin for at least 12 weeks in 10 double-blind, placebo-controll
studies evaluating the effects of TRADJENTA on glycemic control. The overall ethnic/racial distribution in these studies was 69% White, 29%
and included 16% Hispanic/Latino patients. Fifty two percent of patients were male. Patients had an overall mean age of 57 years (range 2
an active (glimepiride)-controlled study of 104 weeks' duration was conducted in 1551 patients with type 2 diabetes who had inadequate

Effect of Coadministered Drugs o
Dosing of Coadm

In vivo Assessment of Drug Interactions
Strong inducers of CYP3A4 or P-gp
such drugs, an alternative to linagliptin is
YP3A4, CYP2C9, CYP2C8, P-gp and organi
kinetic studies.

Linagliptin is a P-glycoprotein (P-gp)
interaction studies, linagliptin is consi
CYP3A4, 2C9, 2C19, 2D6, 2

metformin, and a placebo-controlled study of 52 weeks' duration was conducted in 133 patients with type 2 diabetes and severe chronic renal impairment (eGFR <30 mL/min).

In patients with type 2 diabetes, treatment with TRADJENTA produced clinically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) compared with placebo.

14.1 Monotherapy

A total of 730 patients with type 2 diabetes participated in 2 double-blind, placebo-controlled studies, one of 18 weeks' and another of 24 weeks' duration, to evaluate the efficacy and safety of TRADJENTA monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent and underwent a diet, exercise, and drug washout period of about 6 weeks that included an open-label placebo run-in during the last 2 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week, open-label, placebo run-in period. In the 18-week study, only patients ineligible for metformin were recruited. In the 18-week study, 76 patients were randomized to placebo and 151 to TRADJENTA 5 mg; in the 24-week study, 167 patients were randomized to placebo and 336 to TRADJENTA 5 mg. Patients who failed to meet specific glycemic goals during the 18-week study received rescue therapy with pioglitazone and/or insulin; metformin rescue therapy was used in the 24-week trial.

Treatment with TRADJENTA 5 mg daily provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 4). In the 18-week study, 12% of patients receiving TRADJENTA 5 mg and 18% who received placebo required rescue therapy. In the 24-week study, 10.2% of patients receiving TRADJENTA 5 mg and 20.9% of patients receiving placebo required rescue therapy. The improvement in A1C compared with placebo was not affected by gender, age, race, prior antihyperglycemic therapy, baseline BMI, or a standard index of insulin resistance (HOMA-IR). As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with TRADJENTA appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, the changes from baseline in A1C were -0.4% and -0.4%, respectively, for those given TRADJENTA, and 0.1% and 0.3%, respectively, for those given placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 4 Glycemic Parameters in Placebo-Controlled Monotherapy Studies of TRADJENTA*

	18-Week Study		24-Week Study	
	TRADJENTA 5 mg	**Placebo**	**TRADJENTA 5 mg**	**Placebo**
A1C (%)				
Number of patients	n = 147	n = 73	n = 333	n = 163
Baseline (mean)	8.1	8.1	8.0	8.0
Change from baseline (adjusted mean***)	-0.4	0.1	-0.4	0.3
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.9, -0.3)	--	-0.7 (-0.9, -0.5)	--
Patients [n (%)] achieving A1C <7%**	32 (23.5)	8 (11.8)	77 (25)	17 (12)
FPG (mg/dL)				
Number of patients	n = 138	n = 66	n = 318	n = 149
Baseline (mean)	178	176	164	166
Change from baseline (adjusted mean***)	-13	7	-9	15
Difference from placebo (adjusted mean) (95% CI)	-21 (-31, -10)	--	-23 (-30, -16)	--
2-hour PPG (mg/dL)				
Number of patients	Data not available	Data not available	n = 67	n = 24
Baseline (mean)	--	--	258	244
Change from baseline (adjusted mean***)	--	--	-34	25
Difference from placebo (adjusted mean) (95% CI)	--	--	-58 (-82, -34)	--

*Full analysis population using last observation on study
**18-week study: Placebo, n=68; TRADJENTA, n=136
24-week study: Placebo, n=147; TRADJENTA, n=306
***18-week study. HbA1c: ANCOVA model included treatment, reason for metformin intolerance and number of prior oral anti-diabetic medicine(s) (OADs) as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, reason for metformin intolerance and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.
24-week study. HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

14.2 Combination Therapy

Add-on Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of TRADJENTA in combination with metformin. Patients already on metformin (n = 491) at a dose of at least 1500 mg per day were randomized after completing a 2-week, open-label, placebo run-in period. Patients on metformin and another antihyperglycemic agent (n = 207) were randomized after a run-in period of approximately 6 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either TRADJENTA 5 mg or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.

combination with metformin, TRADJENTA provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 5). e glycemic therapy was used in 7.8% of patients treated with TRADJENTA 5 mg and in 18.9% of patients treated with placebo. A similar decrease in body was observed for both treatment groups.

cemic Parameters in Placebo-Controlled Study for TRADJENTA in Combination with Metformin*

	TRADJENTA 5 mg + Metformin	Placebo + Metformin
	n = 513	n = 175
	8.1	8.0
mean***)	-0.5	0.15
min (adjusted mean) (95% CI)	-0.6 (-0.8, -0.5)	--

in 1000 mg twice daily, n=137; Linagliptin 2.5
1c as continuous covariates. FPG: ANCOVA
ntinuous covariates.
in patients with type 2 diabetes wi
weeks' duration, whereas patients
etformin monotherapy (dose of
(A1C 6.5% to 10%) were r
s ≥8.5%), and the previo
of 1 mg/day and then

-32 -42 (-55, -30) (1)
-60 (-72, -47)

Patients [n (%)] achieving A1C <7%**	127 (26.2)	15 (9.2)
FPG (mg/dL)		
Number of patients	n = 495	n = 159
Baseline (mean)	169	164
Change from baseline (adjusted mean***)	-11	11
Difference from placebo + metformin (adjusted mean) (95% CI)	-21 (-27, -15)	--
2-hour PPG (mg/dL)		
Number of patients	n = 78	n = 21
Baseline (mean)	270	274
Change from baseline (adjusted mean***)	-49	18
Difference from placebo + metformin (adjusted mean) (95% CI)	-67 (-95, -40)	--

*Full analysis population using last observation on study
**TRADJENTA 5 mg + Metformin, n=485; Placebo + Metformin, n=163
***HbA1c: ANCOVA model included treatment and number of prior oral OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

Initial Combination Therapy with Metformin

A total of 791 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in the 24-week, randomized, double-blind, portion of this placebo-controlled factorial study designed to assess the efficacy of TRADJENTA as initial therapy with metformin. Patients on an antihyperglycemic agent (52%) underwent a drug washout period of 4 weeks' duration. After the washout period and after completing a 2-week single-blind placebo run-in period, patients with inadequate glycemic control (A1C ≥7.0% to ≤10.5%) were randomized. Patients with inadequate glycemic control (A1C ≥7.5% to <11.0%) not on antihyperglycemic agents at study entry (48%) immediately entered the 2-week, single-blind, placebo run-in period and then were randomized. Randomization was stratified by baseline A1C (<8.5% vs ≥8.5%) and use of a prior oral antidiabetic drug (none vs monotherapy). Patients were randomized in a 1:2:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Approximately equal numbers of patients were randomized to receive initial therapy with 5 mg of TRADJENTA once daily, 500 mg or 1000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with sulfonylurea, thiazolidinedione, or insulin rescue therapy.

Initial therapy with the combination of linagliptin and metformin provided significant improvements in A1C and fasting plasma glucose (FPG) compared to placebo, to metformin alone, and to linagliptin alone (Table 6).

The adjusted mean treatment difference in A1C from baseline to week 24 (LOCF) was -0.5% (95% CI -0.7, -0.3; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to metformin 1000 twice daily; -1.1% (95% CI -1.4, -0.9; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to TRADJENTA 5 mg once daily; -0.6% (95% CI -0.8, -0.4; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to metformin 500 mg twice daily; and -0.8% (95% CI -1.0, -0.6; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to TRADJENTA 5 mg once daily.

Lipid effects were generally neutral. No meaningful change in body weight was noted in any of the 6 treatment groups.

Table 6 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin and Metformin, Alone and in Combination in Randomized Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise**

	Placebo	**TRADJENTA 5 mg Once Daily***	**Metformin 500 mg Twice Daily**	**Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily**	**Metformin 1000 mg Twice Daily**	**Linagliptin 2.5 mg Twice Daily* + Metformin 1000 mg Twice Daily**
A1C (%)						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean****)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients [n (%)] achieving A1C <7%***	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG (mg/dL)						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	203	195	191	199	191	196
Change from baseline (adjusted mean****)	10	-9	-16	-33	-32	-49
Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

*Total daily dose of TRADJENTA is equal to 5 mg
**Full analysis population using last observation on study
***Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 twice daily, n=136; Metformin 1000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1000 mg twice daily, n=138
****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Active-Controlled Study vs Glimepiride in Combination with Metformin

The efficacy of TRADJENTA was evaluated in a 104-week, double-blind, glimepiride-controlled, non-inferiority study in patients with type 2 diabetes with in glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks' duration, whereas patients pre metformin and one additional antihyperglycemic agent entered a run-in treatment period of 6 weeks' duration with metformin monotherapy (dose of ≥ washout of the other agent. After an additional 2-week placebo run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were ra addition of TRADJENTA 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), and the previo drugs (metformin alone vs metformin plus one other OAD). Patients receiving glimepiride were given an initial dose of 1 mg/day and then

Glycemic Parameters in Placebo-Co

mean***)
(adjusted mean)

with type 2 diabetes weefo
6 weeks on metformin (at a dose of at least 1,
administered once daily. Patients who failed t
In combination with metformin, TRADJENTA
Rescue glycemic therapy was used in 7.8% of pa
ight was observed for both treatment groups.

next 12 weeks to a maximum dose of 4 mg/day as needed to optimize glycemic control. Thereafter, the glimepiride dose was to be kept constant, except for down-titration to prevent hypoglycemia.

After 52 and 104 weeks, TRADJENTA and glimepiride both had reductions from baseline in A1C (52 weeks: -0.4% for TRADJENTA, -0.6% for glimepiride; 104 weeks: -0.2% for TRADJENTA, -0.4% for glimepiride) from a baseline mean of 7.7% (Table 7). The mean difference between groups in A1C change from baseline was 0.2% with 2-sided 97.5% confidence interval (0.1%, 0.3%) for the intent-to-treat population using last observation carried forward. These results were consistent with the completers analysis.

Table 7 Glycemic Parameters at 52 and 104 Weeks in Study Comparing TRADJENTA to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

	Week 52		Week 104	
	TRADJENTA 5 mg + Metformin	**Glimepiride + Metformin (mean Glimepiride dose 3 mg)**	**TRADJENTA 5 mg + Metformin**	**Glimepiride + Metformin (mean Glimepiride dose 3 mg)**
A1C (%)				
Number of patients	n = 764	n = 755	n = 764	n = 755
Baseline (mean)	7.7	7.7	7.7	7.7
Change from baseline (adjusted mean****)	-0.4	-0.6	-0.2	-0.4
Difference from glimepiride (adjusted mean) (97.5% CI)	0.2 (0.1, 0.3)	--	0.2 (0.1, 0.3)	--
FPG (mg/dL)				
Number of patients	n = 733	n = 725	n = 733	n = 725
Baseline (mean)	164	166	164	166
Change from baseline (adjusted mean****)	-8*	-15	-2†	-9
Hypoglycemia incidence (%)***				
Number of patients	n = 776	n = 775	n = 776	n = 775
Incidence****	5.3 *	31.1	7.5 *	36.1

*p<0.0001 vs glimepiride; †p=0.0012 vs glimepiride
**Full analysis population using last observation on study
***Hypoglycemic incidence included both asymptomatic events (not accompanied by typical symptoms and plasma glucose concentration of ≤70 mg/dL) and symptomatic events with typical symptoms of hypoglycemia and plasma glucose concentration of ≤70 mg/dL.
****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. Hypoglycemia incidence (%): Cochran-Mantel-Haenszel test was performed on the patient population contained in the treated set, to compare the proportion of patients with hypoglycemic events between patients treated with linagliptin and patients treated with glimepiride.

Patients treated with linagliptin had a mean baseline body weight of 86 kg and were observed to have an adjusted mean decrease in body weight of 1.1 kg at 52 weeks and 1.4 kg at 104 weeks. Patients on glimepiride had a mean baseline body weight of 87 kg and were observed to have an adjusted mean increase from baseline in body weight of 1.4 kg at 52 weeks and 1.3 kg at 104 weeks (treatment difference p<0.0001 for both timepoints).

Add-On Combination Therapy with Pioglitazone
A total of 389 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of TRADJENTA in combination with pioglitazone. Therapy was stopped in patients on oral antihyperglycemic therapy for a period of 6 weeks (4 weeks followed by a 2-week, open-label, placebo run-in period). Drug-naïve patients entered directly into the 2-week placebo run-in period. After the run-in period, patients were randomized to receive either TRADJENTA 5 mg or placebo, both in addition to pioglitazone 30 mg daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured were A1C and FPG.

In initial combination with pioglitazone 30 mg, TRADJENTA 5 mg provided statistically significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 8). Rescue therapy was used in 7.9% of patients treated with TRADJENTA 5 mg/pioglitazone 30 mg and 14.1% of patients treated with placebo/pioglitazone 30 mg. Patient weight increased in both groups during the study with an adjusted mean change from baseline of 2.3 kg and 1.2 kg in the TRADJENTA 5 mg/pioglitazone 30 mg and placebo/pioglitazone 30 mg groups, respectively (p = 0.0141).

Table 8 Glycemic Parameters in Placebo-Controlled Study for TRADJENTA in Combination Therapy with Pioglitazone*

	TRADJENTA 5 mg + Pioglitazone	**Placebo + Pioglitazone**
A1C (%)		
Number of patients	n = 252	n = 128
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean**)	-1.1	-0.6
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-0.5 (-0.7, -0.3)	--
Patients [n (%)] achieving A1C <7%	108 (42.9)	39 (30.5)
FPG (mg/dL)		
Number of patients	n = 243	n = 122
Baseline (mean)	188	186
Change from baseline (adjusted mean**)	-33	-18
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-14 (-21, -7)	--

*Full analysis population using last observation on study
**HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Sulfonylureas
...e 2 diabetes participated in an 18-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of ...h sulfonylurea (SU). Patients on sulfonylurea monotherapy (n = 142) were randomized after completing a 2-week, single-blind, ...ulfonylurea plus one additional oral antihyperglycemic agent (n = 103) were randomized after a wash-out period of 4 weeks and a

...with oral drugs participated in a randomized, ... over 24 weeks. Randomization was stratified ... oral antidiabetic drugs (none, metformin ... including 709 patients with renal ... study. Patients entered a 2 week placebo run- ... a ... ml/min). Patients who failed to meet ... background therapy. Following the ... tazone ... once daily. Patients who failed to meet ... or placebo, administered once daily. Patients who failed to meet ... A ... f treatment. ... significant improvements in ... ...s for patients treated with ... insulin combined with ... mean change from base... ...h sulfonylurea ... weight from base...

2-week, single-blind, placebo run-in period. Patients were randomized to the addition of TRADJENTA 5 mg or to placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea, TRADJENTA provided statistically significant improvements in A1C compared with placebo following 18 weeks' treatment; the improvements in FPG observed with TRADJENTA were not statistically significant compared with placebo (Table 9). Rescue therapy was used in 7.6% of patients treated with TRADJENTA 5 mg and 15.9% of patients treated with placebo. There was no significant difference between TRADJENTA and placebo in body weight.

Table 9 Glycemic Parameters in Placebo-Controlled Study for TRADJENTA in Combination with Sulfonylurea*

	TRADJENTA 5 mg + SU	**Placebo + SU**
A1C (%)		
Number of patients	n = 158	n = 82
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean***)	-0.5	-0.1
Difference from placebo + SU (adjusted mean) (95% CI)	-0.5 (-0.7, -0.2)	--
Patients [n (%)] achieving A1C <7%**	23 (14.7)	3 (3.7)
FPG (mg/dL)		
Number of patients	n = 155	n = 78
Baseline (mean)	180	171
Change from baseline (adjusted mean***)	-8	-2
Difference from placebo + SU (adjusted mean) (95% CI)	-6 (-17, 4)	--

SU = sulfonylurea
*Full analysis population using last observation on study
**TRADJENTA 5 mg + SU, n=156; Placebo + SU, n=82
***HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates

Add-On Combination Therapy with Metformin and a Sulfonylurea
A total of 1058 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of TRADJENTA in combination with a sulfonylurea and metformin. The most common sulfonylureas used by patients in the study were: glimepiride (31%), glibenclamide (26%), and gliclazide (26%, not available in the United States). Patients on a sulfonylurea and metformin were randomized to receive TRADJENTA 5 mg or placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea and metformin, TRADJENTA provided statistically significant improvements in A1C and FPG compared with placebo (Table 10). In the entire study population (patients on TRADJENTA in combination with sulfonylurea and metformin), a mean reduction from baseline relative to placebo in A1C of -0.6% and in FPG of -13 mg/dL was seen. Rescue therapy was used in 5.4% of patients treated with TRADJENTA 5 mg and in 13% of patients treated with placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 10 Glycemic Parameters in Placebo-Controlled Study for TRADJENTA in Combination with Metformin and Sulfonylurea*

	TRADJENTA 5 mg + Metformin + SU	**Placebo + Metformin + SU**
A1C (%)		
Number of patients	n = 778	n = 262
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean***)	-0.7	-0.1
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.7, -0.5)	--
Patients [n (%)] achieving A1C <7%**	217 (29.2)	20 (8.1)
FPG (mg/dL)		
Number of patients	n = 739	n = 248
Baseline (mean)	159	163
Change from baseline (adjusted mean***)	-5	8
Difference from placebo (adjusted mean) (95% CI)	-13 (-18, -7)	--

SU = sulfonylurea
*Full analysis population using last observation on study
**TRADJENTA 5 mg + Metformin + SU, n=742; Placebo + Metformin + SU, n=247
***HbA1c: ANCOVA model included treatment as class-effects and baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Add-On Combination Therapy with Insulin
A total of 1261 patients with type 2 diabetes inadequately controlled on basal insulin alone or basal insulin in combination with oral drugs participated in a randomized, double-blind placebo-controlled trial designed to evaluate the efficacy of TRADJENTA as add-on therapy to basal insulin over 24 weeks. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), renal function impairment status (based on baseline eGFR), and concomitant use of oral antidiabetic drugs (none, metformin only, pioglitazone only, metformin + pioglitazone). Patients with a baseline A1C of ≥7% and ≤10% were included in the study including 709 patients with renal impairment (eGFR <90 mL/min), most of whom (n=575) were categorized as mild renal impairment (eGFR 60 to <90 mL/min). Patients entered a 2 week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or pioglitazone background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of either 5 mg of TRADJENTA or placebo, administered once daily. Patien[illegible] were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 24 weeks of treatment. Patients who failed to meet s[illegible] glycemic goals during the double-blind treatment period were rescued by increasing background insulin dose.

TRADJENTA used in combination with insulin (with or without metformin and/or pioglitazone), provided statistically significant improvements in A1[illegible] compared to placebo (Table 11) after 24 weeks of treatment. The mean total daily insulin dose at baseline was 42 units for patients treated with TR[illegible] units for patients treated with placebo. Background baseline diabetes therapy included use of: insulin alone (16.1%), insulin combined with m[illegible] insulin combined with metformin and pioglitazone (7.4%), and insulin combined with pioglitazone only (1%). The mean change from base[illegible] dose of insulin was +1.3 IU in the placebo group and +0.6 IU in the TRADJENTA group. The mean change in body weight from baseli[illegible]

Difference from baseline (adjusted mean***)
Patients [n (%)] achieving A1C <7%
FPG (mg/dL)
Number of patients
Baseline (mean)
Change from baseline (adjusted mean***)
Difference from placebo (adjusted mean**)
Patients [n (%)] achieving A1C <7%
Difference from baseline (adjusted mean***)
Difference from placebo + pioglitazone (adjusted mean**)
Sulfonylureas
Type 2 diabetes participat[illegible]
sulfonylurea (SU)
plus o[illegible]
analysis population using last observation
ANCOVA model included treatment and number of prior OA

the two treatment groups. The rate of hypoglycemia, defined as all symptomatic or asymptomatic episodes with a self-measured blood glucose was also similar in both groups (21.4% TRADJENTA; 22.9% placebo) in the first 24 weeks of the study.

Table 11 Glycemic Parameters in Placebo-Controlled Study for TRADJENTA in Combination with Insulin*

	TRADJENTA 5 mg + Insulin	Placebo + Insulin
A1C (%)		
Number of patients	n = 618	n = 617
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean***)	-0.6	0.1
Difference from placebo (adjusted mean) (95% CI)	-0.7 (-0.7, -0.6)	--
Patients [n (%)] achieving A1C <7%**	116 (19.5)	48 (8.1)
FPG (mg/dL)		
Number of patients	n = 613	n = 608
Baseline (mean)	147	151
Change from baseline (adjusted mean***)	-8	3
Difference from placebo (adjusted mean) (95% CI)	-11 (-16, -6)	--

*Full analysis population using last observation carried forward (LOCF) method on study
**TRADJENTA + Insulin, n=595; Placebo + Insulin, n=593
***HbA1c: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

The difference between treatment with linagliptin and placebo in terms of adjusted mean change from baseline in HbA1c after 24 weeks was comparable for patients with no renal impairment (eGFR ≥90 mL/min, n=539), with mild renal impairment (eGFR 60 to <90 mL/min, n= 565), or with moderate renal impairment (eGFR 30 to <60 mL/min, n=124).

14.3 Renal Impairment

A total of 133 patients with type 2 diabetes participated in a 52 week, double-blind, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of TRADJENTA in patients with both type 2 diabetes and severe chronic renal impairment. Participants with an estimated (based on the four variables modified diet in renal disease [MDRD] equation) GFR value of <30 mL/min were eligible to participate in the study. Randomization was stratified by baseline HbA1c (≤8% and >8%) and background antidiabetic therapy (insulin or any combination with insulin, SU or glinides as monotherapy and pioglitazone or any other antidiabetics excluding any other DPP-4 inhibitors). 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. At baseline in this trial, 62.5% of patients were receiving insulin alone as background diabetes therapy, and 12.5% were receiving sulfonylurea alone.

After 12 weeks of treatment, TRADJENTA 5 mg provided statistically significant improvement in A1C compared to placebo, with an adjusted mean change of -0.6% compared to placebo (95% confidence interval -0.9, -0.3) based on the analysis using last observation carried forward (LOCF). With adjustments in antidiabetic background therapy after the initial 12 weeks, efficacy was maintained for 52 weeks, with an adjusted mean change from baseline in A1C of -0.7% compared to placebo (95% confidence interval -1.0, -0.4) based on analysis using LOCF.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADJENTA tablets are available as light red, round, biconvex, bevel-edged, film-coated tablets containing 5 mg of linagliptin. TRADJENTA tablets are debossed with "D5" on one side and the Boehringer Ingelheim logo on the other side.

They are supplied as follows:
Bottles of 30 (NDC 0597-0140-30)
Bottles of 90 (NDC 0597-0140-90)
Cartons containing 10 blister cards of 10 tablets each (10 x 10) (NDC 0597-0140-61), institutional pack.
If repackaging is required, dispense in a tight container as defined in USP.

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Store in a safe place out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Medication Guide
Instruct patients to read the Medication Guide before starting TRADJENTA therapy and to reread it each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Inform patients of the potential risks and benefits of TRADJENTA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

s that acute pancreatitis has been reported during postmarketing use of TRADJENTA. Inform patients that persistent severe abdominal pain, sometimes eek, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue TRADJENTA their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

symptoms of heart failure. Before initiating TRADJENTA, patients should be asked about a history of heart failure or other risk factors severe renal impairment. Instruct patients to contact their healthcare provider as soon as possible if they experience symptoms of ortness of breath, rapid increase in weight or swelling of the feet *[see Warnings and Precautions (5.2)]*.

Hypoglycemia
Inform patients that the incidence of hypoglycemia is increased when TRADJENTA is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Hypersensitivity Reactions
Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of TRADJENTA. If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking TRADJENTA and seek medical advice promptly.

Severe and Disabling Arthralgia
Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.5)]*.

Bullous Pemphigoid
Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.6)]*.

Missed Dose
Instruct patients to take TRADJENTA only as prescribed. If a dose is missed, advise patients not to double their next dose.

Blood Glucose and A1C Monitoring
Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels, with a goal of decreasing these levels toward the normal range. A1C monitoring is especially useful for evaluating long-term glycemic control.

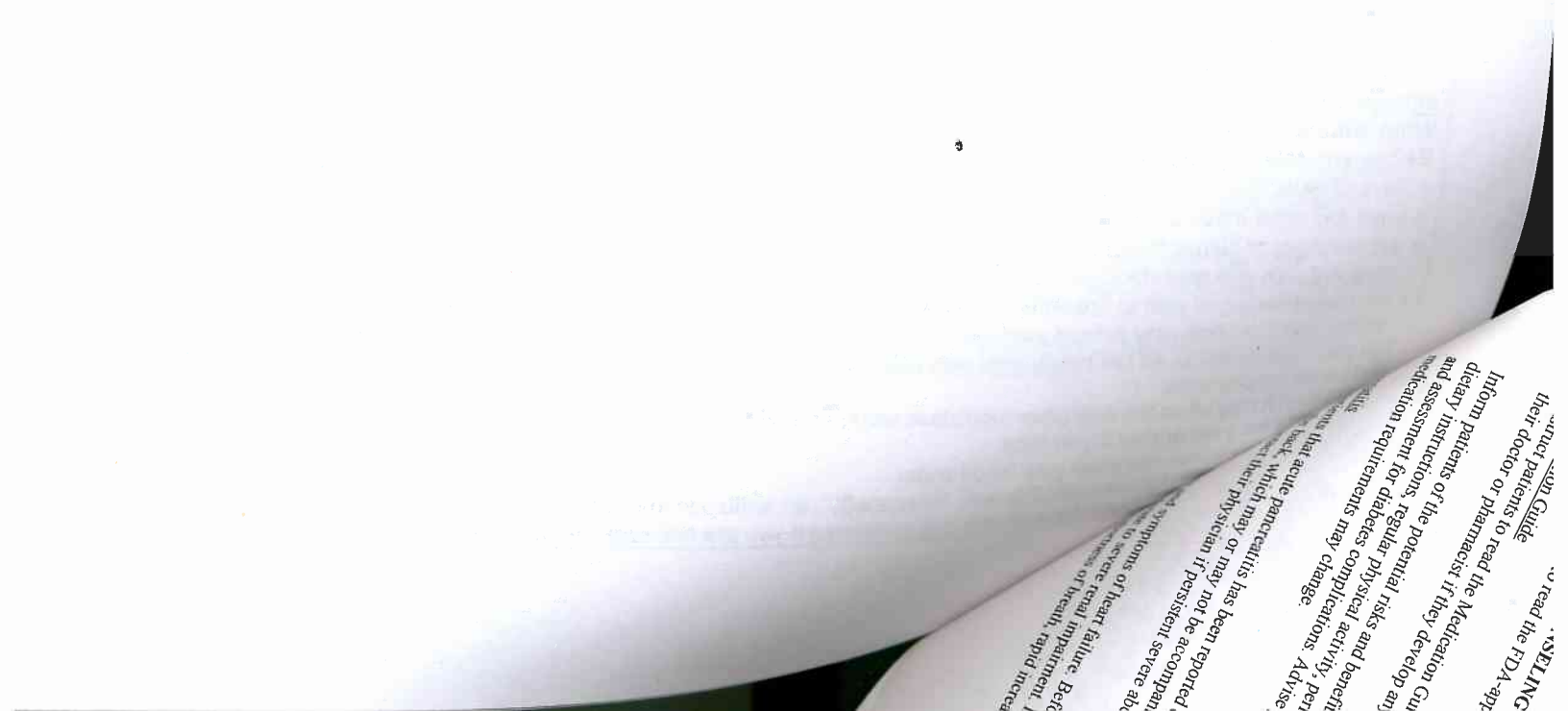
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MEDICATION GUIDE
TRADJENTA® (TRAD gen ta)
(linagliptin)
Tablets

Read this Medication Guide carefully before you start taking TRADJENTA and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. If you have any questions about TRADJENTA, ask your doctor or pharmacist.

What is the most important information I should know about TRADJENTA?
Serious side effects can happen to people taking TRADJENTA, including:

- **Inflammation of the pancreas (pancreatitis)** which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

Before you start taking TRADJENTA, tell your doctor if you have ever had:

- inflammation of your pancreas (pancreatitis)
- a history of alcoholism
- stones in your gallbladder (gallstones)
- high blood triglyceride levels

Stop taking TRADJENTA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

- **Heart failure.** Heart failure means your heart does not pump blood well enough.
  Before you start taking TRADJENTA, tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor right away if you have any of the following symptoms:
  - increasing shortness of breath or trouble breathing, especially when you lie down
  - swelling or fluid retention, especially in the feet, ankles or legs
  - an unusually fast increase in weight
  - unusual tiredness

  These may be symptoms of heart failure.

What is TRADJENTA?

- TRADJENTA is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- TRADJENTA is not for people with type 1 diabetes.
- TRADJENTA is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- If you have had pancreatitis in the past, it is not known if you have a higher chance of getting pancreatitis while you take TRADJENTA.

It is not known if TRADJENTA is safe and effective in children under 18 years of age.

Who should not take TRADJENTA?
Do not take TRADJENTA if you:

- are allergic to linagliptin or any of the ingredients in TRADJENTA. See the end of this Medication Guide for a complete list of ingredients in TRADJENTA.

Symptoms of a serious allergic reaction to TRADJENTA may include:

- skin rash, itching, flaking or peeling
- raised red patches on your skin (hives)
- swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowing
- difficulty with swallowing or breathing

If you have any of these symptoms, stop taking TRADJENTA and contact your doctor or go to the nearest hospital emergency room right away.

What should I tell my doctor before using TRADJENTA?
Before you take TRADJENTA, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if TRADJENTA will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if TRADJENTA passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take TRADJENTA.
- **our doctor about all the medicines you take,** including prescription and over-the-counter medicines, vitamins, al supplements.
- TA may affect the way other medicines work, and other medicines may affect how TRADJENTA works.
- **your doctor if you take**
- that can lower your blood sugar
- Rimactane®, Rifater®, Rifamate®)*, an antibiotic that is used to treat tuberculosis
- macist for a list of these medicines if you are not sure if your medicine is one that is listed above.

ides. Do
even if they have the same
f you would like more
about TRADJENTA that is
ww.TRADJENTA.com) or call
06.

6JP6-W69P

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take TRADJENTA?

- Take 1 tablet 1 time each day with or without food.
- Your doctor will tell you when to take TRADJENTA.
- Talk with your doctor if you do not understand how to take TRADJENTA.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of TRADJENTA at the same time.
- Your doctor may tell you to take TRADJENTA along with other diabetes medicines. Low blood sugar can happen more often when TRADJENTA is taken with certain other diabetes medicines. See **"What are the possible side effects of TRADJENTA?"**
- If you take too much TRADJENTA, call your doctor or Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking TRADJENTA.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of TRADJENTA?

TRADJENTA may cause serious side effects, including:

- See **"What is the most important information I should know about TRADJENTA?"**
- **low blood sugar (hypoglycemia).** If you take TRADJENTA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take TRADJENTA. Signs and symptoms of low blood sugar may include:
  - o headache
  - o drowsiness
  - o weakness
  - o dizziness
  - o confusion
  - o irritability
  - o hunger
  - o fast heart beat
  - o sweating
  - o feeling jittery
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions can happen after your first dose or up to 3 months after starting TRADJENTA. Symptoms may include:
  - o swelling of your face, lips, throat, and other areas on your skin
  - o difficulty with swallowing or breathing
  - o raised, red areas on your skin (hives)
  - o skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking TRADJENTA and call your doctor or go to the nearest hospital emergency room right away.

- **Joint pain.** Some people who take medicines called DPP-4 inhibitors like TRADJENTA, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors like TRADJENTA, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking TRADJENTA.

The most common side effects of TRADJENTA include stuffy or runny nose and sore throat, cough, **and** diarrhea

These are not all the possible side effects of TRADJENTA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRADJENTA?

- Store TRADJENTA between 68°F and 77°F (20°C and 25°C).

Keep TRADJENTA and all medicines out of the reach of children.

General information about the safe and effective use of TRADJENTA.

Medicines are sometimes prescribed for purposes other than those listed in Medication Guides. Do not use TRADJENTA for a condition for which it was not prescribed. Do not give TRADJENTA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about TRADJENTA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TRADJENTA that is written for health professionals.

For more information, go to www.TRADJENTA.com (or scan the code below to go to www.TRADJENTA.com) or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906.

What are the ingredients in TRADJENTA?
Active Ingredient: linagliptin
Inactive Ingredients: mannitol, pregelatinized starch, corn starch, copovidone, and magnesium stearate. The film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and red ferric oxide.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and/or the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.
The main goal of treating diabetes is to lower your blood sugar to a normal level. High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.
Talk to your doctor about how to prevent, recognize, and take care of low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and other problems you have because of your diabetes.

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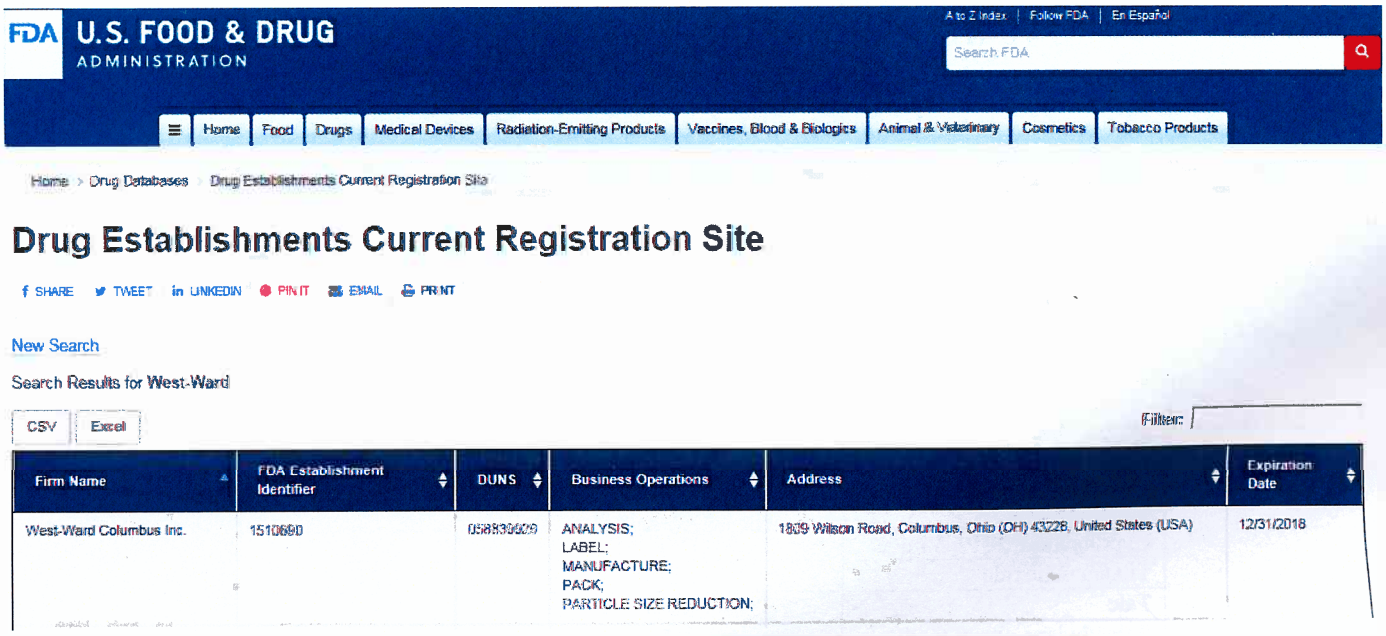
IT6174IH142017

This Medication Guide has been approved by the U. S. Food and Drug Administration. Revised: August 2017

6JP6-W69P

Boehringer Ingelheim

FDA Drug Firm Registrations are electronically filed and this is a screen print of the status from the U.S. Food and Drug Administration website: http://www.accessdata.fda.gov/scripts/cder/drls/default.cfm.



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Firm Name	FDA Establishment Identifier	DUNS	Business Operations	Address	Expiration Date
West-Ward Columbus Inc.	1510690	058830609	ANALYSIS; LABEL; MANUFACTURE; PACK; PARTICLE SIZE REDUCTION;	1809 Wilson Road, Columbus, Ohio (OH) 43228, United States (USA)	12/31/2018

6JP6-W69P

Boehringer Ingelheim

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. certifies that the following information is "true" as it applies to the Qualitative and Quantitative Composition of the following drug product:

Tradjenta® (linagliptin) 5 mg Tablets, NDA 201280
Qualitative and Quantitative Composition

Component	Reference to Standards	Concentration (coated tablet)
Tablet Core		
Linagliptin	Company Standard	5.000
Mannitol	USP	130.900
Pregelatinized starch	NF	18.000
Corn starch	NF	18.000
Copovidone	NF	5.400
Magnesium stearate	NF	2.700
Water, purified*	USP	--
Coating		
Opadry® Pink (02F34337)	Company Standard	5.000
Water, purified*	USP	
Opadry® Pink (02F34337)		
Hypromellose 2910, 5 mPas	USP	2.500
Titanium dioxide	USP	1.250
Talc	USP	0.875
Polyethylene glycol 6000	NF	0.250
Red ferric oxide	NF	0.125

* Removed during processing, does not appear in the final product.

We also certify that the Shelf-Life for this product is 36 months and Storage Conditions at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) as approved in **Tradjenta® (linagliptin) 5 mg Tablets NDA 201280.**

Signed: _____ Date: 04/09/2018

Dr. Xiaohui Mei, Associate Director, CMC, Regulatory Affairs

State of Connecticut)
) ss: Ridgefield
County of Fairfield)

On this 9th day of April 2018, before me, Kristin E. Snow, the undersigned officer, personally appeared Dr. Xiaohui Mei, who acknowledged himself to be a Associate Director of CMC Regulatory Affairs of Boehringer Ingelheim Pharmaceuticals, Inc., a corporation, and that he as such Associate Director, being authorized so to do executed the foregoing instrument for the purposes therein contained, by signing the name of the corporation by himself as Associate Director.

In witness whereof I hereunto set my hand.

_____
Kristin E. Snow
Notary Public
My Commission Expires: March 31, 2022

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APOSTILLE

(Convención de La Haya de Octubre 5 de 1961)

1. País: Estados Unidos

   Este documento público

2. Ha sido firmado por: Andrei Perlloni
3. Actuando en su capacidad de Jefe de Sucursal, Oficina de Cumplimiento de Exportaciones e Importaciones de Medicamentos
4. Lleva el sello/estampa de: Departamento de Salud y Servicios Humanos de los Estados Unidos

Certifica

5. En Washington D.C.
6. En Julio 5 de 2018
7. Por *Funcionario Asistente de Autenticaciones, Departamento de Estado de los Estados Unidos*
8. No. 18046402-3
9. Sello/Estampa:
10. Firma:

    (Firmado en el original)

    Chana M Turner

Sergio Eleuterio Latorre Mendoza
Traductor e Interprete Oficial
Resol. No. 2839 Minjusticia 1991

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Departamento de Alimentos y Medicamentos de los Estados Unidos

Centro para la Evaluación e Investigación de Medicamentos

10903 New Hampshire Ave, Silver Spring, MD 20993, Estados Unidos

CDERExportCertificateProgram@fda.hhs.gov – Teléfono: (301) 796-4950

Certificado de Producto Farmacéutico – Producto Medicinal Aprobado

Certificado No. **6JP6-W69P** Fecha de Emisión del Certificado: **Mayo 29 de 2018**

Fecha de Expiración del Certificado: **Mayo 28 de 2020**

País importador: **COLOMBIA** País exportador: **ESTADOS UNIDOS**

1.	Nombre comercial, internacional o nacional no exclusivo (si aplica) del medicamento y presentación: **TRADJENTA®, Tablet**
1.1.	Ingrediente(s) activo(s) y cantidad(es) por dosis (se prefiere la composición cuantitativa completa): **linagliptina** 5 MG
1.2.	¿Se encuentra este producto autorizado para ser colocado en el mercado para uso en el país exportador? **Si**
1.3.	¿Se encuentra este producto actualmente en el mercado del país exportador? **Si**
2.A1.	Número de licencia y fecha de emisión: **201280 05/02/2011**
2.A2.	Nombre y dirección del poseedor de la licencia: **Boehringer-Ingelheim Inc., 900 Ridgebury Road, Ridgefield, CT 06877 Estados Unidos**
2.A3.	Estatus del propietario de la licencia del producto: **Ninguno**
2.A3.1.	Nombre y dirección del fabricante: **West-Ward Columbus Inc., 1809 Wilson Road, OH 43228 Estados Unidos**
2.A4.	¿Se ha enmendado un resumen base para la aprobación? **Si**
2.A5.	¿La información adjunta del producto está completa y es consistente con la licencia? **Si**
2.A6.	Nombre y dirección del solicitante del certificado (Si es diferente del propietario de la licencia): **Boehringer-Ingelheim Inc., 900 Ridgebury Road, Ridgefield, CT 06877 Estados Unidos**
2.B4.	Observaciones: **Fabricante API: Boehringer Ingelheim Pharma GmbH and Co. KG, Binger Strasse 173, Ingelheim am Rhein, Rheinland-Pfalz 55216 ALEMANIA. Nombre comercial internacional: Tradjenta; Nombre Comercial Local: Trayenta**
3.	¿La autoridad certificadora organiza inspecciones periódicas de la planta de fabricación donde se produce la presentación? **Si**
3.1.	Periodicidad de las inspecciones (años): **De acuerdo con la sección 510(h)(3) de la Ley Federal de Alimentos, Medicamentos & Cosméticos, las inspecciones tendrán lugar de acuerdo con un cronograma basado en el riesgo**
3.2.	¿Ha sido inspeccionado el fabricante de este tipo de presentación? **Si**
3.3.	¿Las instalaciones y operaciones cumplen con las BPF de acuerdo con lo recomendado por la OMS? (Las BPFs incluyen 21 Código de Regulaciones Federales partes 210, 211 o ICH Q7A): **Si, al momento de la inspección, el sitio cumple con FDA cGDP**
3.4.	¿La información enviada por el solicitante satisface a la autoridad certificadora en todos los aspectos de la fabricación del producto hechos por otra parte? **Si**

Sergio Eleuterio Latorre Mendoza
Traductor e Interprete Oficial
Resol. No. 2839 Minjusticia 1991

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(Firmado en el original)

Andrei Perlloni, Director

División de Importaciones, Exportaciones y Retiros del Mercado

Oficina de Seguridad de Medicamentos, Integridad & Respuesta

(Nota del traductor: Adjunto se encuentra un sello del Departamento de Salud y Servicios Humanos de los Estados Unidos)

Lo anterior cumple con el formato recomendado por la Organización Mundial de la Salud (OMS), formato revisado Octubre 1 de 1997. Página Web: www.who.int

Yo, Sergio Latorre, por medio de la presente, Cerífico que la anterior es una traducción verdadera y precisa del documento original escrito en inglés. Bogotá, julio 25 de 2018

Sergio Eleuterio Latorre Mendoza
Traductor e Interprete Oficial
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