

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

-----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 combination with insulin (1.2)

-----DOSAGE AND ADMINISTRATION-----

- The recommended dose of TRADJENTA is 5 mg once daily. 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 urticaria, angioedema, or bronchial hyperreactivity (4)

-----WARNINGS AND PRECAUTIONS-----

- When used with an insulin secretagogue (e.g., sulfonylurea), consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia (5.1)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA or any other antidiabetic drug (5.2)

-----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)
- Pancreatitis was reported more often in patients randomized to linagliptin (1 per 538 person years versus zero in 433 person years for comparator) (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-----

P-glycoprotein/CYP 3A4 inducer: The efficacy of TRADJENTA may be reduced when administered in combination (e.g., with rifampin). Use of alternative treatments is strongly recommended. (7.1)

-----USE IN SPECIFIC POPULATIONS-----

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

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

1.2 Important Limitations of Use

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

TRADJENTA has not been studied in combination with insulin.

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 a Sulfonylurea

When TRADJENTA is used in combination with an insulin secretagogue (e.g., sulfonylurea), a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia [see *Warnings and Precautions (5.1)*].

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 urticaria, angioedema, or bronchial hyperreactivity [see *Adverse Reactions 6.1*].

5 WARNINGS AND PRECAUTIONS

5.1 Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues 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)*]. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with TRADJENTA.

5.2 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The safety of linagliptin has been evaluated in over 4000 patients with type 2 diabetes in clinical trials, including 12 placebo-controlled studies and 1 active-controlled study with glimepiride.

TRADJENTA 5 mg once daily was studied as monotherapy in two placebo-controlled trials of 18- and 24-weeks duration. Five placebo-controlled trials investigated linagliptin in combination with other oral anti-glycemic agents: two with metformin (12- and 24-weeks treatment duration); one with a sulfonylurea (18-weeks treatment duration); one with metformin and sulfonylurea (24-week treatment duration); and one with pioglitazone (24-week treatment duration). In placebo-controlled clinical trials, adverse reactions that occurred in $\geq 5\%$ of patients receiving TRADJENTA (n = 2566) and more commonly than in patients given placebo (n = 1183) included nasopharyngitis (5.8% vs 5.5%). Adverse reactions reported in $\geq 2\%$ of patients treated with TRADJENTA 5 mg daily as monotherapy or in combination with pioglitazone, sulfonylurea, or metformin and at least 2-fold more commonly than in patients treated with placebo are shown in Table 1.

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

	Monotherapy*		Combination with Metformin [#]		Combination with SU		Combination with Metformin + SU		Combination with Pioglitazone	
	TRADJENTA n (%)	Placebo n (%)	TRADJENTA n (%)	Placebo n (%)	TRADJENTA n (%)	Placebo n (%)	TRADJENTA n (%)	Placebo n (%)	TRADJENTA n (%)	Placebo n (%)
	n = 765	n = 458	n = 590	n = 248	n = 161	n = 84	n = 791	n = 263	n = 259	n = 130
Nasopharyngitis	--	--	--	--	7 (4.3)	1 (1.2)	--	--	--	--
Hyperlipidemia	--	--	--	--	--	--	--	--	7 (2.7)	1 (0.8)
Cough	--	--	--	--	--	--	19 (2.4)	3 (1.1)	--	--
Hypertriglyceridemia [†]	--	--	--	--	4 (2.4)	0 (0.0)	--	--	--	--
Weight increased	--	--	--	--	--	--	--	--	6 (2.3)	1 (0.8)

SU = sulfonylurea

* Pooled data from 7 studies

[#] Pooled data from 2 studies

[†] Includes reports of hypertriglyceridemia (n = 2; 1.2%) and blood triglycerides increased (n = 2; 1.2%)

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

Other adverse reactions reported in clinical studies with treatment of TRADJENTA were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity), and myalgia. In the clinical trial program, pancreatitis was reported in 8 of 4687 patients (4311 patient years of exposure) while being treated with TRADJENTA compared with 0 of 1183 patients (433 patient years of exposure) treated with placebo. Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycemia

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

Laboratory Tests

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

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

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 CYP 3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with P-gp or CYP 3A4 inducer [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness of TRADJENTA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients ($n = 4040$) in clinical studies of TRADJENTA, 1085 patients were 65 years and over, while 131 patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. While this and other reported clinical experience have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is recommended in this population.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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.

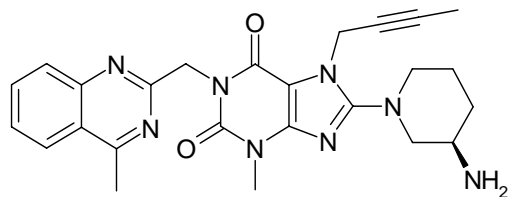
In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis.

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-quinazoliny)methyl]-

The empirical formula is C₂₅H₂₈N₈O₂ 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 a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4 but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

Plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. The prolonged elimination phase does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady state compared with the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Plasma AUC of linagliptin increased in a less than dose proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Absorption

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

Distribution

The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75%-89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metabolism

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

Excretion

Following administration of an oral [¹⁴C]-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.

Results of this study, supported by results of population pharmacokinetic analyses, indicate that no dose adjustment is recommended in patients with renal impairment.

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. No dose adjustment of linagliptin is necessary in patients with hepatic impairment.

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

No dose adjustment is recommended based on age, as 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

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.

Table 2 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug*	Dosing of Linagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0	
			AUC [†]	Cmax
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
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
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 Cmax=Emax for pharmacodynamic endpoints

INR = International Normalized Ratio

PT = Prothrombin Time

QD = once daily

BID = twice 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, and pioglitazone therapy. TRADJENTA has not been studied in combination with insulin.

There were approximately 3800 patients with type 2 diabetes randomized in 8 double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of linagliptin on glycemic control. The overall ethnic/racial distribution in these studies was approximately 65% White, 33% Asian, and 2% Black, and included 14% Hispanic/Latino patients. Fifty-two percent of patients were male. Patients had an overall mean age of 57 years (range 20 to 80 years). In addition, an active (glimepiride)-controlled study of 52-weeks duration was conducted in over 1500 patients with type 2 diabetes who had inadequate glycemic control on metformin.

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-week and another of 24-week 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 linagliptin 5 mg; in the 24-week study 167 patients were randomized to placebo and 336 to linagliptin 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 (%) achieving A1C <7%	41 (28%)	11 (15%)	77 (25%)	17 (12%)
FPG (mg/dL)				
Number of patients	n = 138	n = 66	n = 318	n = 149
Baseline (mean)	178.4	175.6	164	166
Change from baseline (adjusted mean)	-13.3	7.2	-8.5	14.8
Difference from placebo (adjusted mean) (95% CI)	-20.5 (-31.1, -9.9)		-23.3 (-30.4, -16.3)	
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)			-33.5	24.9
Difference from placebo (adjusted mean) (95% CI)			-58.4 (-82.3, -34.4)	

*Full analysis population using last observation on study

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 linagliptin 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 linagliptin 5 mg or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.

In combination with metformin, linagliptin provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 5). Rescue glycemic therapy was used in 7.8% of patients treated with linagliptin 5 mg and in 18.9% of patients treated with placebo. The mean change from baseline in A1C of TRADJENTA/metformin versus placebo/metformin over the 24-week treatment period is shown in Figure 2. A similar decrease in body weight was observed for both treatment groups.

Table 5 Glycemic Parameters in Placebo-Controlled Study for TRADJENTA in Combination with Metformin*

	TRADJENTA 5 mg + Metformin	Placebo + Metformin
A1C (%)		
Number of patients	n = 513	n = 175
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean)	-0.5	0.15

Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6 (-0.8, -0.5)	
Patients (%) achieving A1C <7%	145 (28.3)	20 (11.4)
FPG (mg/dL)		
Number of patients	n = 495	n = 159
Baseline (mean)	169.0	163.8
Change from baseline (adjusted mean)	-10.7	10.5
Difference from placebo + metformin (adjusted mean) (95% CI)	-21.1 (-27.3, -15.0)	
2-hour PPG (mg/dL)		
Number of patients	n = 78	n = 21
Baseline (mean)	270	274
Change from baseline (adjusted mean)	-48.9	18.3
Difference from placebo + metformin (adjusted mean) (95% CI)	-67.1 (-94.7, -39.6)	

*Full analysis population using last observation on study

Active-Controlled Study vs Glimepiride in Combination with Metformin

The efficacy of linagliptin is being evaluated in a 104-week double-blind, glimepiride-controlled non-inferiority study in type 2 diabetic patients with insufficient glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks duration, whereas patients pretreated with metformin and one additional antihyperglycemic agent entered a run-in treatment period of 6 weeks duration with metformin monotherapy (dose of ≥ 1500 mg per day) and 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 randomized 1:1 to the addition of linagliptin 5 mg once daily or glimepiride. Patients receiving glimepiride were given an initial dose of 1 mg/day and then electively titrated over the 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 weeks, linagliptin and glimepiride both had reductions from baseline in A1C (-0.4% for linagliptin, -0.6% for glimepiride) from a baseline mean of 7.7% (Table 6). The mean difference between groups in HbA1c 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.

Patients treated with linagliptin exhibited a significant mean decrease from baseline body weight compared to a significant weight gain in patients administered glimepiride (-1.1 kg vs +1.4 kg, $p < 0.0001$).

Table 6 Glycemic Parameters at 52 Weeks in Study Comparing TRADJENTA to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

	TRADJENTA 5 mg + Metformin	Glimepiride + Metformin (mean Glimepiride dose 3 mg)
A1C (%)		
Number of patients	n = 766	n = 761
Baseline (mean)	7.7	7.7
Change from baseline (adjusted mean)	-0.4	-0.6
Difference from glimepiride (adjusted mean) (97.5% CI)	--	0.2 (0.1, 0.3)
FPG (mg/dL)		
Number of patients	n = 736	n = 731
Baseline (mean)	164.1	166.6
Change from baseline (adjusted mean)	-8.6	-16.2
Hypoglycemia incidence (%)		
Number of patients	n = 778	N = 781
Incidence	5.4*	31.8

* $p < 0.0001$ vs glimepiride

**Full analysis population using last observation on study

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 linagliptin 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 in to the 2-week placebo run-in period. After the run-in period patients were randomized to receive either linagliptin 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, linagliptin 5 mg provided statistically significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 7). Rescue therapy was used in 7.9% of patients treated with linagliptin 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 linagliptin 5 mg/pioglitazone 30 mg and placebo/pioglitazone 30 mg groups, respectively ($p = 0.0141$).

Table 7 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)	188.4	186.4
Change from baseline (adjusted mean)	-32.6	-18.4
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-14.2 (-21.1, -7.3)	

*Full analysis population using last observation on study

Add-On Combination with Sulfonylureas

A total of 245 patients with type 2 diabetes participated in an 18-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of linagliptin in combination with sulfonylurea (SU). Patients on sulfonylurea monotherapy (n = 142) were randomized after completing a 2-week single-blind placebo run-in period. Patients on a sulfonylurea plus one additional oral antihyperglycemic agent (n = 103) were randomized after a wash-out period of 4 weeks and a 2-week single-blind placebo run-in period. Patients were randomized to the addition of linagliptin 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, linagliptin provided statistically significant improvements in A1C compared with placebo following 18 weeks treatment; the improvements in FPG observed with linagliptin were not statistically significant compared with placebo (Table 8). Rescue therapy was used in 7.6% of patients treated with linagliptin 5 mg and 15.9% of patients treated with placebo. There was no significant difference between linagliptin and placebo in body weight.

Table 8 Glycemic Parameters at 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 (%) achieving A1C <7%	15.2	3.7
FPG (mg/dL)		
Number of patients	n = 155	n = 78
Baseline (mean)	180	171
Change from baseline (adjusted mean)	-8.2	-1.8
Difference from placebo + SU (adjusted mean) (95% CI)	-6.4 (-17.2, 4.3)	--

SU = sulfonylurea

*Full analysis population using last observation on study

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 linagliptin 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 linagliptin 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 9). 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 -12.7 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 9 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%	243 (31.2)	24 (9.2)
FPG (mg/dL)		
Number of patients	n = 739	n = 248
Baseline (mean)	159.2	162.6
Change from baseline (adjusted mean)	-4.6	8.1
Difference from placebo (adjusted mean) (95% CI)	-12.7 (-18.1, -7.3)	

SU = sulfonylurea

*Full analysis population using last observation on study

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)

Bottles of 1000 (NDC 0597-0140-10)

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

See FDA-Approved Patient Labeling.

17.1 Instructions

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.

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

Instruct patients to read the Patient Information 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.

17.2 Laboratory Tests

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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10007237/01

PATIENT INFORMATION

TRADJENTA™ (TRAD gen ta) (linagliptin) Tablets

Read this Patient Information 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.

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).
- It is not known if TRADJENTA is safe and effective when used with insulin.
- It is not known if TRADJENTA is safe and effective in children.

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 leaflet for a complete list of ingredients in TRADJENTA.

Symptoms of a serious allergic reaction to TRADJENTA are:

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

What should I tell my doctor before using TRADJENTA?

Before you take TRADJENTA, tell your doctor if you:

- have any other medical conditions
- are pregnant or planning 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.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

TRADJENTA may affect the way other medicines work, and other medicines may affect how TRADJENTA works.

Especially tell your doctor if you take

- other medicines that can lower your blood sugar
- rifampin (Rifadin®, Rimactane®, Rifater®, Rifamate®)*, an antibiotic that is used to treat tuberculosis

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is one that is listed above.

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 TRADJENTA 1 time each day exactly as your doctor tells you to take it.
- Talk with your doctor if you do not understand how to take TRADJENTA.
- Your doctor will tell you when to take TRADJENTA.
- Take TRADJENTA with or without food.
- 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.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- 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:

- **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:
 - headache
 - drowsiness
 - weakness
 - dizziness
 - confusion
 - irritability
 - hunger
 - fast heart beat
 - sweating
 - feeling jittery

The most common side effects of TRADJENTA include:

- stuffy or runny nose and sore throat

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

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

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 at 59°F to 86°F (15°C to 30°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 Patient Information leaflets. 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 Patient Information 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 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.

This Patient Information has been approved by the U. S. Food and Drug Administration.

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Revised May 2011