Brand Name: Tradjenta

Generic Name: Linagliptin

Manufacturer[3,4,5]: Boehringer Ingelheim Pharmaceuticals, Inc

Drug Class[1,2,4]: Antidiabetic agent**,** Dipeptidyl Peptidase-4 (DPP-IV) Inhibitor

Uses[1,2,3,4,5]:

Linagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with noninsulin dependent type 2 diabetes mellitus as monotherapy or combination therapy.

Mechanism of Action:[1,2,3,4,5]

Linagliptin inhibits dipeptidyl peptidase-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are involved in the maintenance of glucose homeostasis. These hormones stimulate the release of insulin in a glucose-dependent manner, by increasing insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. GLP-1 also decreases the glucagon secretion from pancreatic alpha cells, which results in a reduction in hepatic glucose production. Linagliptin inhibits the degradation of these hormones by DPP-4, thereby increasing insulin release in a glucose-dependent manner and decreasing the levels of circulating glucagon. Linagliptin is beneficial in patients with type 2 DM as their GLP-1 concentrations are decreased in response to a meal.

Pharmacokinetics[1,2,3,4,5]:

T_{max}	1.5 hours
Volume of Distribution	1110 L
Half-life	Effective: 12 hours; Terminal: >100 hours
Clearance	70 mL/minute
Protein Binding	70 – 99% (concentration dependent)
Absolute Bioavailability	30%

Metabolism:

Not extensively metabolized
A small fraction is metabolized to a pharmacologically inactive metabolite
Weak to moderate inhibitor of CYP3A4

Elimination:

85% is excreted via the enterohepatic system (80%) or urine (5%)
Over 90% of the drug is excreted unchanged; feces (80%), urine (5%)

Efficacy:

Ring, A., Port, A., Graefe-Mody, E. U., Revollo, I., Iovino, M. and Dugi, K. A. The DPP-4 inhibitor linagliptin does not prolong the QT interval at therapeutic and supratherapeutic doses. British Journal of Clinical Pharmacology. 2011;72:39–50.[6]

Study Design:
Randomized, double-blind, placebo-controlled, 4-period crossover study

Description of Study:
Methods: The study used single oral doses of linagliptin 5 mg, linagliptin 100 mg, moxifloxacin 400 mg, and placebo. Electrocardiogram profiles using triplicates of 12-lead 10-s ECGs were digitally recorded pre- and post-dosing. The primary endpoint was the mean change from baseline (MCfB) of the individually heart rate corrected QT interval (QTcI) between 1 and 4 hours post-drug administration. Plasma concentrations of linagliptin and its metabolite were also measured by blood samples. *Outcome Results:* 43 subjects completed the study as planned, out of the initial 44 subjects entered. No increase in the baseline-adjusted mean QTcI occurred with linagliptin at any time. The placebo-corrected MCfB of QTcI was −1.1 (90% CI −2.7, 0.5) ms for linagliptin 5 mg and −2.5 (–4.1, –0.9) ms for linagliptin 100 mg. These results fall within the non-inferiority margin of 10 ms according to ICH E14. Linagliptin was well tolerated, with no relevant clinical findings at either dose, based on the assessment of ECGs and other safety parameters. Maximum plasma concentrations after administration of 100-mg linagliptin were 24-fold higher than those observed previously for chronic treatment with the therapeutic 5-mg dose. Assay sensitivity was confirmed by a placebo-corrected MCfB of QTcI with moxifloxacin of 6.9 (90% CI 5.4, 8.5) ms.

Limitations:
Although there is some scientific discussion on the clinical interpretation of QT shortening, its impact on clinical outcomes is generally deemed low and intensive investigations of QTc-shortening drugs do not currently seem to be warranted for drug approval. The disadvantage of the study duration of 6 months was considered to be out- weighed by the advantages of intraindividual comparisons that would be possible using this study design, and the minimal pharmacokinetic carry-over observed, combined with the low dropout rate, confirmed the feasibility of this approach. Subjects were recruited from the volunteers' pool of the Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. in Biberach, Germany. The authors are all employees of Boehringer Ingelheim as well, which is the company that sponsored the study.

Conclusion:
Linagliptin 5-mg and 100-mg doses were well tolerated when administered as single doses. There were no clinically significant laboratory abnormalities reported and no clinically relevant abnormalities observed in the ECGs of any of the subjects. Vital signs were normal throughout the study. Tolerability was rated as 'good' for all subjects and treatments by the investigator. The drug-related adverse event most commonly reported was headache, which was observed in all treatment groups. Breast cancer was reported as a serious adverse event and was considered unrelated to study medication by the investigator. Linagliptin does not cause clinically relevant changes of the corrected QT interval with a therapeutic dose and a 20-fold therapeutic dose. The 20-fold therapeutic dose of linagliptin was safe and well tolerated. Therapeutic and significantly supratherapeutic exposure to linagliptin is not associated with QT interval prolongation.

Forst, T., Uhlig-Laske, B., Ring, A., Ritzhaupt, A., Graefe-Mody, U., Dugi, K. A. The oral DPP-4 inhibitor linagliptin significantly lowers HbA1c after 4 weeks of treatment in patients with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism. 2011; 13: 542-50.[7]

Study Design:
Phase IIA randomized, double-blind, parallel, placebo-controlled

Description of Study:
Methods: Subjects received linagliptin 2.5, 5 or 10 mg or placebo once-daily for 28 days, after screening and a 14-day washout period. *Outcome Results:* A total of 77 patients entered the study; linagliptin: 61 and placebo: 16. Four patients withdrew. Exposure, maximum and trough plasma concentrations of linagliptin increased less than dose-proportionally. There was little evidence of drug accumulation. Rapid and sustained inhibition of dipeptidyl peptidase-4 reached 91–93% across linagliptin doses at steady state. At the end of the 24 hour dosing interval, inhibition was still high (82–90%). There were increases in plasma glucagon-like peptide-1 after 28 days of dosing. All linagliptin doses resulted in statistically significant decreases of the area under the glucose curve following a meal tolerance test on day 29 (24 hours after the last study drug intake). After 28 days of treatment with linagliptin the placebo-corrected mean change in HbA1c (median baseline 7.0%) was −0.31% (2.5-mg dose), −0.37% (5-mg dose) and −0.28% (10-mg dose). The frequency of adverse events was similar for linagliptin (31%) and placebo (34%). There were no notable safety concerns.

Limitations:
There was an imbalance in the number of ADTs taken by the patients prior to the start of study, because there was no stratification for ADTs during randomization. A higher percentage of patients, who washed out two ADTs, was being randomized to the linagliptin 10-mg dose group compared with the other dose groups and placebo. Therefore, the number of previous ADTs was taken into account as a factor in the statistical analysis of the pharmacodynamic endpoints.The planned sample size was not based on a power calculation, as all statistical analyses were exploratory in nature. Group sizes were based on feasibility and were considered sufficient for the exploratory evaluation of safety, pharmacokinetics and pharmacodynamics of multiple doses of linagliptin. Minor deviations from the reference range were noted in several clinical laboratory parameters, but these were not considered to be clinically relevant with the exception of one patient in the 5-mg dose group, who showed a clinically relevant increase in blood uric acid. The short duration of the study period (4 weeks) is a problem when evaluating reductions in HbA1c levels. Generally, determination of the change in HbA1c is made after sufficient time to allow turnover of the red blood cell stock, at least 3 months. All the authors (except Forst) are employees of Boehringer Ingelheim, the company that sponsored the study. The study protocol was designed by the authors who were also responsible for data collection, analysis and reporting of results.

Conclusion:
This study showed the effect of the potent and selective DPP-4 inhibitor linagliptin on glycemic control in patients with T2DM without any major or minor hypoglycemic episodes. In addition, the data suggest that in future studies dedicated to identifying the optimal dose for the treatment of patients with T2DM, the dose range should include, but not be limited to, 2.5–10 mg linagliptin, as tested in the present study. Linagliptin had a safety and tolerability profile similar to placebo in T2DM patients.

Del Prato, S., Barnett, A. H., Huisman, H., Neubacher, D., Woerle, H.-J., Dugi, K. A. Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes, Obesity and Metabolism. 2011; 13: 258–267. [8]

Study Design:
Phase III multicenter, randomized, parallel, placebo-controlled

Description of Study:
Methods: Compared linagliptin 5 mg once daily (n = 336) with placebo (n = 167) for 24 weeks in type 2 diabetes patients. Before randomization, patients pretreated with one oral antidiabetic underwent a washout period of 6 weeks, which included a placebo run-in period during the last 2 weeks. Patients previously untreated with an oral antidiabetic underwent a 2-week placebo run-in period. The primary endpoint was the change in HbA1c from baseline after 24 weeks of treatment. *Outcome Results*: Linagliptin treatment resulted in a placebo-corrected change in HbA1c from baseline of −0.69% ($p < 0.0001$) at 24 weeks. In patients with baseline HbA1c ≥ 9.0%, the adjusted reduction in HbA1c was 1.01% ($p < 0.0001$). Patients treated with linagliptin were more likely to achieve a reduction in HbA1c of ≥0.5% at 24 weeks than those in the placebo arm (47.1 and 19.0%, respectively; odds ratio, OR = 4.2, $p < 0.0001$). Fasting plasma glucose improved by −1.3 mmol/l ($p < 0.0001$) with linagliptin vs. placebo, and linagliptin produced an adjusted mean reduction from baseline after 24 weeks in 2-h postprandial glucose of −3.2 mmol/l ($p < 0.0001$). Statistically significant and relevant treatment differences were observed for proinsulin/insulin ratio ($p = 0.025$), Homeostasis Model Assessment-%B ($p = 0.049$) and disposition index ($p = 0.0005$). Mild or moderate renal impairment did not influence the trough plasma levels of linagliptin.

Limitations:
The washout period was only 6 weeks, so that there was not a stable baseline in the patients who had received a prior oral antidiabetic. As a consequence, there was a continuous rise in HbA1c over time in the placebo group and a smaller drop from baseline in the linagliptin group. This may be caused by incomplete washout of the effect of prior treatment on HbA1c, because it is known that the effect of treatment on HbA1c may last up to 12 weeks. However, the difference between placebo and linagliptin HbA1c levels with and without washout was comparable, supporting the concept of sustained efficacy.This study was of short duration and thus the results of chronic treatment with linagliptin cannot be determined. Chronic treatment with some diabetes therapies is associated with the progressive loss of glycemic control. Studies of longer duration are needed to test whether DPP-4 inhibitors, through their actions on β-cells, may attenuate the loss of glycaemic control over time that has been seen in diabetes patients treated with established medications.

Conclusion:
Linagliptin 5 mg once daily for 24 weeks produced significant, clinically meaningful and sustained improvements in glycemic control compared with placebo. Changes in HbA1c, FPG and 2hPPG reflected the improved pre- and postprandial glycemic control induced by linagliptin treatment. Enhancement of parameters of β-cell function may help to sustain glycemic control. Linagliptin monotherapy resulted in a safety profile comparable to that of placebo, with a very low risk of hypoglycemia and no clinically significant changes in body weight or waist circumference. Linagliptin may be less likely to accumulate in renally impaired type 2 diabetes patients, since only a minor proportion of a linagliptin dose is renally excreted. Overall, this study suggests that linagliptin could help meet the need for an innovative antidiabetic to improve the management of the increasing number of patients with type 2 diabetes.

Contraindications[1,2,3,4,5]:

Hypersensitivity Reaction:
Hypersensitivity to linagliptin or any component of the formulation, such as urticaria, angioedema, or bronchial hyperreactivity.

Precautions[1,2,3,4,5]:

Insulin
Linagliptin has not been studied in combination with insulin.

Insulin secretagogues:
Concomitant use of an insulin secretagogue may increase the risk of hypoglycemia. Monitor blood glucose closely; dosage reduction of secretagogues may be required.

Type 1 Diabetes/Diabetic Ketoacidosis:
The use of linagliptin in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis is not effective and should not be used.

Adverse Effects[1,2,3,4,5]:

Hypoglycemia (monotherapy 7.6%; combination therapy 22.9%)
Backache (6.4%)
Arthralgia (5.7%)
Headache (5.7%)
Nasopharyngitis (4.3% to 5.8%)
Hyperlipidemia (2.7%)
Increased uric acid level (2.7%)
Hypertriglyceridemia (2.4%)
Cough (2.4%)
Weight increase (2.3%)
Hypersensitivity reaction (<1%)
Pancreatitis (<1%)
Myalgia (<1%)

Drug Interactions[1,2,3,4,5]:

ACE inhibitors: may enhance hypoglycemic effects.

Alcohol (ethanol): may cause variable effects on glycemic control.

Angiotensin II receptor antagonists: may enhance hypoglycemic effects

Anti-retroviral protease inhibitors: may cause insulin resistance.

Atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone): may cause hyperglycemia, hyperglycemic states, and diabetic coma.

Baclofen: may increase blood glucose.

Beta-blockers: affects body's ability to regulate blood glucose.

Bexarotene: may cause hyperglycemia or hypoglycemia

Bortezomib: may cause hypoglycemia and hyperglycemia

Carbonic anhydrase inhibitors: may cause glycosuria and hyperglycemia

Cisapride, metoclopramide, and tegaserod: may enhance gastric emptying

Clonidine: may potentiate or weaken hypoglycemic effects

Corticosteroids: may decrease hypoglycemic effects

Cyclosporine: may cause hyperglycemia

CYP 3A4/strong p-glycoprotein Inducers: efficacy may be reduced

Dextrothyroxine: may decrease hypoglycemic effects

Diazoxide: may increase blood glucose

Disopyramide: may enhance hypoglycemic effects

Diuretics: (Thiazide diuretics and triamterene) may decrease hypoglycemic effects

Estrogens, progestins, or oral contraceptives: may decrease hypoglycemic effects

Fenfluramine and dexfenfluramine: may potentiate drug action

Fibric acid derivatives: may enhance hypoglycemic effects

Fluoxetine: may enhance hypoglycemic effects

Gatifloxacin: contraindicated for use in patients with diabetes mellitus

Glucagon: may cause an increase in blood glucose concentrations

Guanethidine: may enhance hypoglycemic effects

Isoniazid (INH): may increase blood glucose concentrations (rare)

Lithium: may cause variable effects on glycemic control

Mecasermin, recombinant, rh-IGF-1 and mecasermin rinfabate (rh-IGF-1/rh-IGFBP-3): may cause hypoglycemia

Monoamine oxidase inhibitors (MAOIs): may stimulate insulin secretion

Niacin (nicotinic acid): may interfere with glucose metabolism and cause hyperglycemia.

Octreotide: may produce hypoglycemia

Pegvisomant: may increase insulin sensitivity

Pentamidine: may cause hypoglycemia acutely, followed by hyperglycemia

Phenothiazines (chlorpromazine): may increase blood glucose

Phenytoin, fosphenytoin, or ethotoin: may decrease hypoglycemic effects

Quinolones: may cause hyperglycemia and hypoglycemia

Reserpine: may mask the signs and symptoms of hypoglycemia.

Salicylates: may increase insulin secretion and decrease blood glucose

Somatropin, rh-GH, and growth hormone: cause increases in blood glucose

Sulfonamides: may induce hypoglycemia by increasing the secretion of insulin

Sulfonylureas: increase risk of hypoglycemia

Sympathomimetics: may increase blood glucose concentrations

Tacrolimus: may cause hyperglycemia

Testosterone: may cause hypoglycemia or hyperglycemia

Thyroid hormones: may reduce glucose-lowering effects

Dosing/Administration[1,2,3,4,5]:

Adult:

Usual dosage: 5 mg once daily (with or without food)

Elderly:

No dose adjustment is recommended.

Children:

Safety and effectiveness have not been established.

Renal function impairment:

No dose adjustment is recommended.

Hepatic function impairment:

No dose adjustment is recommended.

Use in Special circumstances:

Pregnancy:

Pregnancy risk category B. Only use during pregnancy if clearly needed. No adequate and well-controlled studies in pregnant women exist.

Lactation:

Excretion into breast milk is unknown. The manufacturer advises cautious use by a mother who is breast-feeding, as many drugs are excreted in breast milk.

Conclusion:

Tradjenta (linagliptin) is a DPP-IV inhibitor used as monotherapy or combination therapy for the treatment of noninsulin dependent type 2 diabetes mellitus. Other available medications in this drug class are Januvia and Onglyza. In general, the drug works to reduce plasma glucose levels and hemoglobin A1c. Therapy with this medication is quite convenient, as it is taken as a single fixed dose once daily without regard to food. Additionally, it does not require dose adjustments for organ impairment. These characteristics make Tradjenta a desirable choice in the early management of Type 2 diabetes. However, this drug is not a suitable option for use in patients with type 1 diabetes mellitus, diabetic ketoacidosis, or those using insulin. Overall, Tradjenta appears to be a safe and effective DPP-IV inhibitor and should be utilized as an adjunct to lifestyle modifications to improve glycemic control in noninsulin dependent patients with type 2 diabetes mellitus.

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Prepared by: Natalie Heckathorn, Doctor of Pharmacy Candidate