CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 201280/S-002

Trade Name: **TRADJENTA**

Generic Name: **Linagliptin**

Sponsor: **Boehringer Ingelheim Pharmaceuticals, Inc.**

Approval Date: 05/22/2012

Indications: 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

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201280/S-002

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Lee-Sogaard:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on July 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tradjenta (linagliptin) tablets, 5 mg.

We acknowledge receipt of your amendments dated September 21, and 22, and November 16, 2011, and March 9, and April 19, 2012. We also acknowledge receipt of your email dated May 21, 2012, that includes the agreed-upon labeling.

This "Prior Approval" supplemental new drug application provides for modifications to the Patient Package Insert (PPI), changes to the **ADVERSE REACTIONS** section of the Highlights of Prescribing Information section and changes to the **ADVERSE REACTIONS, USE IN SPECIFIC POPULATIONS, OVERDOSAGE, CLINICAL PHARMACOLOGY, AND CLINICAL STUDIES** of the Full Prescribing Information sections of the Tradjenta package insert (PI).

These changes are based on the safety and efficacy results from trial 1218.46, entitled "A Phase 3, randomized, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naive or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycemic control." The efficacy and safety of trial 1218.46 was fully reviewed under the Jentadueto (linagliptin/metformin fixed-dose combination) NDA (201281).

We have completed our review of the supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Package Insert (PI)
Patient Package Insert (PPI)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
05/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

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 treated with linagliptin (1 per 562 patient years versus zero in 589 patient years for placebo) (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/CYP3A4 inducer: The efficacy of TRADJENTA may be reduced when administered in combination (e.g., with rifampin). Use of alternative treatments is strongly recommended. (7.1)

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

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

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

Revised: xx/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

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

1.2 Important Limitations of Use

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

TRADJENTA has not been studied in 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 an Insulin Secretagogue (e.g., 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 evaluation of linagliptin 5 mg once daily in patient with type 2 diabetes is based on 13 placebo-controlled trials and 1 active-controlled study. In the 13 placebo-controlled studies, a total of 2994 patients were randomized and treated with TRADJENTA 5 mg daily and 1546 with placebo. The mean exposure across studies was 21.4 weeks. The maximum follow-up was 78 weeks.

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 antihyperglycemic agents: 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); and one with pioglitazone (24 weeks' treatment duration).

In placebo-controlled clinical trials, adverse reactions that occurred in ≥5% of patients receiving TRADJENTA (n = 2994) and more commonly than in patients given placebo (n = 1546) included nasopharyngitis (5.9% vs 4.8%). Adverse reactions reported in ≥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 ≥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* n (%)		**Combination with Metformin# n (%)**		**Combination with SU n (%)**		**Combination with Metformin + SU n (%)**		**Combination with Pioglitazone n (%)**	
	TRADJENTA n = 907	**Placebo n = 530**	**TRADJENTA n = 876**	**Placebo n = 539**	**TRADJENTA n = 161**	**Placebo n = 84**	**TRADJENTA n = 791**	**Placebo n = 263**	**TRADJENTA n = 259**	**Placebo 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 8 studies
#Pooled data from 3 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 ≥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 5115 patients (4499 patient years of exposure) while being treated with TRADJENTA compared with 0 of 1546 patients (589 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, 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 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 792 (22.9%) patients reported hypoglycemia compared with 39 of 263 (14.8%) 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 ≥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 CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a P-gp or CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

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

Linagliptin administered during the period of organogenesis was not teratogenic at doses up to 30 mg/kg in the rat and 150 mg/kg in the rabbit, or approximately 49 and 1943 times the clinical dose based on AUC exposure. Doses of linagliptin causing maternal toxicity in the rat and the rabbit also caused developmental delays in skeletal ossification and slightly increased embryofetal loss in 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
There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of TRADJENTA; 1085 (27%) were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

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

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

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

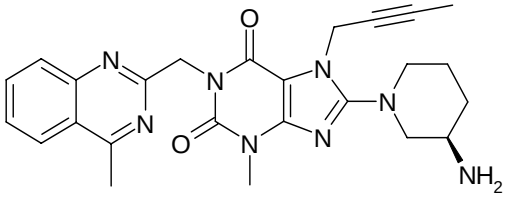
During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of TRADJENTA (equivalent to 120 times the recommended daily dose) there were no dose-related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

11 DESCRIPTION

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

Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta-cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha-cells, resulting in a reduction in hepatic glucose output.

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

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

Absorption

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

Distribution

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

Metabolism

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

Excretion

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

Specific Populations

Renal Impairment

An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes mellitus and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes mellitus and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

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

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

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

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

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

A total of 3017 patients with type 2 diabetes were randomized and exposed to linagliptin for at least 12 weeks in 9 double-blind, placebo-controlled clinical efficacy studies evaluating the effects of linagliptin on glycemic control. The overall ethnic/racial distribution in these studies was 66% White, 33% Asian, and 1% 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 1559 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 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 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 [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

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. 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 [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.

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 linagliptin 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 linagliptin 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 linagliptin 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, -0.5; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to linagliptin 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	**Linagliptin 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 + met 500 twice daily, n=136; Metformin 1000mg twice daily, n=137; Linagliptin 2.5 mg twice daily and Metformin 1000 mg twice daily, n=138.

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 patients with type 2 diabetes 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/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 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.

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 7 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	167
Change from baseline (adjusted mean)	-9	-16
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 into 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 8). 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 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

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 9). 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 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.

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 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 -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 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

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)
Cartons containing 10 blister cards of 10 tablets each (10 x 10) (NDC 0597-0140-61)
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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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, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine 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: x 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 201280/S-002

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	4/25/2012
From	Jean-Marc Guettier, MDCM
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	201280 002
Applicant	Boehringer Ingelheim
Date of Submission	7/22/2011
PDUFA Goal Date	5/22/2012
Proprietary Name / Established (USAN) names	linagliptin/tradjenta
Dosage forms / Strength	5 mg tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
Recommended:	Approval

Cross Discipline Team Leader Review Template

1. Introduction

Linagliptin is a once-daily, oral, dipeptidyl-peptidase-IV (DPP4) inhibitor approved in May 2011 as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes. The current supplement focuses on trial 1218.46, the pivotal trial used to establish the efficacy and safety of the fixed-dose combination product linagliptin/metformin HCL (NDA#: 201281) approved January 2012. The sponsor uses data from this study to update the adverse reactions and clinical studies sections of the current label. (b) (4)

2. Background

The supplement contains one full study report for Trial 1218.46. Trial 1218.46 was a 24-week randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of twice daily co-administration of linagliptin 2.5 mg + metformin 500 mg and of twice daily co-administration of linagliptin 2.5 mg + metformin 1000 mg to the individual components of the co-administered drugs (i.e., metformin 500 mg twice daily, metformin 1000 mg twice daily, linagliptin 5 mg once daily) and to placebo. The efficacy and safety findings for this trial were fully reviewed in NDA 201281 (refer to Dr. Ilan Irony's CDTL memorandum for details). No additional efficacy and safety data for trial 1218.46 were provided with this supplement.

In a 23-page "clinical overview statement" document (Source eCTD; NDA201280 section 1.11.3) the sponsor submits a report of safety analyses focused on myalgia in a dataset of pooled placebo controlled trials which includes the addition of data from trial 1218.46. No report of analyses for uric acid levels were submitted at the time of supplement filing. These were requested from the sponsor and received in the form of a 7-page 'clinical overview' document (Source eCTD; NDA201280 section 1.11.3) on September 9, 2011. Dr. Kwon focused her review on these two documents. In my review of the source documents described above, I found that the hyperlinks to cross-referenced material did not work and that appendices to the original documents were not attached. Information requests alerting the sponsor of these omissions were sent. Additional exposure data in the clinical overview documents did not appear to be limited to study 1218.46. Information requests were sent to the sponsor requesting clarification of exposure data. The sponsor could not provide clarification during this review cycle and opted to submit this additional information as responses to other supplements currently under review (S003, S004).

3. CMC/Device

This supplement does not contain new Chemistry/Manufacturing/Controls (CMC) data.

4. Nonclinical Pharmacology/Toxicology

This supplement does not contain new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

This supplement does not contain new pharmacology/biopharmaceutics data.

6. Clinical Microbiology

This supplement does not contain new clinical microbiology data.

7. Clinical/Statistical- Efficacy

The efficacy of linagliptin 2.5 mg co-administered with metformin 500 mg or 1000 mg orally twice daily was fully reviewed in NDA 201281 (refer to Dr. Ilan Irony's CDTL memorandum for details). In study 1218.46, the sponsor demonstrated that co-administration of linagliptin and metformin resulted in significantly greater reduction in baseline HbA1c than that observed in the arms randomized to linagliptin alone, metformin alone or placebo. Efficacy findings from this supplement formed the basis of approval for the fixed-dose combination product, linagliptin/metformin HCL (Jentadueto™). The sponsor in this supplement updates Section 14 of the full prescribing information for the single entity product, linagliptin, with results from trial 1218.46 to support use of linagliptin as add-on to metformin therapy.

Briefly, trial 1218.46 was a multinational, multicenter, phase 3, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of twice daily (BID) co-administration of linagliptin 2.5 mg+metformin 500 mg, linagliptin 2.5 mg+metformin 1000 mg, to the individual components: metformin 500 mg BID, metformin 1000 mg BID, and linagliptin 5 mg daily. A total of 791 subjects were randomized 1:2 to placebo or to one of the five other active treatment arms.

The primary endpoint was the change in HbA1c at week 24 in the full analysis set population (i.e., intention to treat with LOCF). Clinically meaningful reductions in HbA1c were seen for the combination of linagliptin and metformin when compared to monotherapy treatment.

- The coadministration of linagliptin 2.5 mg and metformin 1000 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.5% [SE=0.11], $p<0.001$) when compared to metformin 1000 mg BID
- The coadministration of linagliptin 2.5 mg and metformin 1000 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -1.1% [SE=0.11], $p<0.0001$) when compared to linagliptin 5 mg daily

- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.6% [SE=0.11], p<0.001) when compared to metformin 500 mg BID
- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.8% [SE=0.11], p<0.0001) when compared to linagliptin 5 mg daily

8. Safety

Refer to Dr. Hyon Kwon's review for the detailed safety findings in this supplement.

Myalgia:

In the linagliptin application, myalgia is a medical concept defined by grouping the following MedDRA preferred terms: muscle tightness, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness and myalgia.

The "SAF-2" dataset pooled all placebo-controlled linagliptin trials performed in T2DM subjects. This dataset was used to perform safety analyses when the original linagliptin application (201280) was filed.

Trials included in "SAF-2" are listed in the sponsor's table below (Source: Table 2 Dr. Kwon's review). In these trials, linagliptin was used as monotherapy or was added to maximally effective doses of one or more oral anti-diabetic agent (pioglitazone, metformin, and/or sulfonylurea). Dr. Kwon describes these trials in details in Table 1 of her review (not shown).

Table 1: Studies included in "SAF-2", NDA 201280

								Patient numbers N (%)		
Safety grouping	Objective	Trial characteristics	Studies	Phase	Treatment duration	Doses	Patients / Healthy subjects	Total (random.)	Linagliptin (treated)	Linagliptin 5 mg (treated)
SAF-2	Safety in patients with T2DM on linagliptin 5 mg	Placebo-controlled trials with lingliptin 5 mg in patients with T2DM	1218.2	I	12 days	1, 2.5, 5, 10 mg	P	48 (100.0)	35 (72.9)	8 (16.7)
			1218.3	I	28 days	2.5, 5, 10 mg	P	77 (100.0)	59 (76.6)	15 (19.5)
			1218.5[o]	II	12 weeks	0.5, 2.5, 5 mg	P	302 (100.0)	170 (56.3)	55 (18.2)
			1218.6[p]	II	12 weeks	1, 5, 10 mg	P	333 (100.0)	197 (59.2)	66 (19.8)
			1218.15	III	24 weeks	5 mg	P	389 (100.0)	259 (66.6)	259 (66.6)
			1218.16	III	24 weeks	5 mg	P	503 (100.0)	336 (66.8)	336 (66.8)
			1218.17	III	24 weeks	5 mg	P	701 (100.0)	523 (74.6)	523 (74.6)
			1218.18	III	24 weeks	5 mg	P	1058 (100.0)	792 (74.9)	792 (74.9)
			1218.23[q]	III	52 weeks[b]	5, 10 mg	P (Japan)	561 (100.0)	319 (56.9)	159 (28.3)
			1218.35	III	18 weeks	5 mg	P	245 (100.0)	161 (65.7)	161 (65.7)
			1218.37	II	4 weeks	5 mg	P	121 (100.0)	40 (33.1)	40 (33.1)
			1218.50	III	18 weeks[e]	5 mg	P	227 (100.0)	151 (66.5)	151 (66.5)
Total patient numbers in SAF-2, N (%)								4565 (100.0)	3042 (66.6)	2565 (56.2)

Source: NDA 201280, SCS, Table 1.1.3:1, page 28

Myalgia was reported in 1.8% (47/2566) and 1.2% (14/1183) of subjects randomized to linagliptin 5 mg and placebo respectively in "SAF-2". The imbalance was more pronounced in the subgroup of placebo-controlled trials where linagliptin was added to other background oral anti-diabetic agents. The table below, taken from Dr. Kwon's review, highlights this finding.

Table 2: Proportion of Subjects Reporting and Adverse Event of Myalgia in Original Safety Dataset (SAF-2)

Trial (Add-on therapy)	Treatment Arm	
	Linagliptin 5 mg	Placebo
1218.05 (none)	0 (0/55)	3% (2/67)
1218.06 (metformin)	4.5% (3/66)	1.4% (1/71)
1218.15 (pioglitazone)	0.4% (1/259)	0.8% (1/130)
1218.16 (none)	1.2% (4/336)	0.6% (1/167)
1218.17 (metformin)	2.3% (12/523)	0.6% (1/177)
1218.18 (metformin+SU)	1.9% (15/792)	0.8% (2/263)
1218.23 (none)	2.5% (4/159)	2.5% (2/80)
1218.35 (SU)	1.9% (3/161)	1.2% (1/84)
1218.50 (none)	3.3% (5/151)	3.9% (3/76)
Total	**1.8% (47/2566)**	**1.2% (14/1183)**

Source: Dr. Kwon's Review
SU =sulfonylurea.

The sponsor had defined adverse reactions as adverse events occurring in greater than 2% of subjects exposed to linagliptin and twice as commonly in the linagliptin arm compared to placebo. The sponsor's definition of an "adverse reaction" for the event of myalgia was satisfied only when trials evaluating linagliptin added to metformin were considered [i.e., 2.5% (15/289) versus 0.8% (2/248): Source NDA 201280, SCS Appendix and ISS, Module 5.3.5.3, Table 5.2.2.10.2]. However imbalances of less than 2-fold not favoring linagliptin were seen when linagliptin was co-administered with both metformin and sulfonylurea and sulfonylurea alone (Refer to Table 5 in Dr. Kwon's review).

In the original pool of safety data (i.e., "SAF-2), no events of mylagia were considered serious, two events led to study discontinuation and no cases of rhabdomyolysis were reported. Dr. Somya Dunn, in her review of NDA 201280, made note of a slight imbalance in subject transitioning from normal to high serum creatinine kinase levels (5.7 versus 4.5% linagliptin versus placebo). Drug-drug interaction studies did not suggest a mechanism to explain the observed imbalance. With regards to myalgia, Section 6.1 of the current linagliptin label reads:

"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."

The sponsor updated the "SAF-2" dataset, at the four month safety update, with information from Trial 1218.46.

To analyze events of myalgia the sponsor used this updated dataset but removed trials 1218.15 (add-on to pioglitazone), 1218.18 (add-on to metformin and sulfonylurea), 1218.35 (add-on to sulfonylurea) from this dataset effectively removing 1202 subjects exposed to the 5 mg dose of linagliptin. The new more limited dataset, is referred to as "4MSU2" (i.e., four months safety update 2). Myalgia analyses were performed according to groups of trials where linagliptin was used either alone (i.e., monotherapy dataset: '4MSU2A') or used as an add-on to metformin only (4MSU2B).

Table 3: Updated Exposure for Linagliptin Monotherapy and Linagliptin Add-on to Metformin Subgroups

Sponsor's Subgroup Nomenclature		"SAF-2" Original Dataset (N)	1218.46 (N)	"SAF-2" + 1218.46 New pooled dataset
Linagliptin Monotherapy	**Linagliptin Monotherapy**	765	142	907
"4MSU2A"	**Placebo Monotherapy**	458	72	530
Linagliptin Add-on to metformin	**Linagliptin added to background metformin**	590	285	875
"4MSU2B"	**Placebo added to background metformin**	248	291	539

No differences in the proportion of subjects reporting myalgia between linagliptin and placebo was observed in the pool of placebo-controlled data where linagliptin was used as monotherapy [i.e., 1.8% (16/907) versus 1.7% (9/530)] for linagliptin and placebo respectively]. In the add-on to metformin pool, a proportionally higher number of individuals exposed to linagliptin reported events of myalgia [i.e., 1.9% (17/875) versus 1.3% (7/539)] for linagliptin and placebo: dataset "MSU-2B").

Dr. Kwon calculated the proportion of subjects with myalgia by adding additional data captured in trial 1218.46 to the entire pool of safety data for placebo controlled trials (i.e., "SAF-2"). The imbalance not favoring linagliptin persists and is similar in magnitude to the labeled imbalance observed in the original NDA [i.e., 1.7% (71/4202) versus 1.2% (24/2023)].

Reviewer Comment: The decision by the sponsor to omit trials in their re-analyses of myalgia across the linagliptin development program was not clear. Myalgia is not a known adverse reaction associated with use of sulfonylurea class drugs and would not be expected to confound the results. The sponsor's internal definition for adverse reactions (i.e., >2% incidence and 2-fold above placebo), is not consistent with the regulatory definition of adverse reaction (i.e., incidence > placebo and plausibly drug related). The imbalance in the overall pool of placebo-controlled trial data is similar to that observed with the original safety dataset. The following information request related to myalgia was sent on April 17th 2012.

(b) (4) ***In your updated pooled placebo controlled safety database (SAF-2 + 1218.46) an imbalance not favoring linagliptin in myalgia adverse event reporting similar to that seen in the original NDA is still seen (1.7 versus 1.2%). You performed several additional subgroup analyses excluding all trials except monotherapy and add-on to metformin trials. We are aware that the imbalance was seen when linagliptin was co-administered with metformin but it is not clear why you excluded trials 1218.18, and 1218.35 from these subgroup analyses since myalgia is not a reported adverse reaction for sulfonylurea drugs. In your pooled placebo-controlled studies (excluding the renal impairment study) and by treatment arm (linagliptin versus placebo) please provide the following;***

> ***Line listing and narratives, by unique subject ID numbers, of serious adverse events in participants having ever reported myalgia as an adverse event***
>
> ***Line listing and narratives , by unique subject ID numbers, of discontinuations in participants having ever reported myalgia as an adverse event***
>
> ***Line listing by participant ID numbers for other clinically significant events (i.e., rhabomyolysis, myopathy, muscle weakness) not captured by the above two categories***
>
> ***The number of participants having ever reported myalgia who also had elevations in creatinine kinase above the upper limit at anytime in the study***
>
> ***Analyze for the presence baseline risk factors (i.e., medications, medical conditions) for myalgia in the linagliptin versus placebo arm***
>
> ***Describe the time course of myalgia in participants who ever reported myalgia"***

Reviewer Comment: The sponsor could not respond within the review cycle, (b) (4)

Increases in Uric Acid Levels

In the initial linagliptin application, serum uric acid elevation was defined as a laboratory value above the upper limit of the reference range (2.5-6.5 mg/dL). Elevation in uric acid was identified as a "Potential Clinically Significant Abnormality" (PCSA)". A PCSA was defined as an event observed to occur more frequently in the linagliptin group and where the difference between linagliptin and placebo exceeded 1%.

Analyses were performed on the pool of placebo controlled studies (SAF-2). At the time of NDA filing uric acid measurements were available for 2489 linagliptin treated subjects and 1140 placebo treated subjects. The frequency (%) and number (N) of individuals with PCSA elevation in uric acid were 2.7% (N=68) and 1.3% (N=15) for linagliptin and placebo respectively. More subjects shifted from baseline normal values to elevated values in the linagliptin compared to the placebo arm (5.5% versus 3.4%). No imbalances in adverse events of gout (0.2% in both treatment arms) or kidney stones (0.3% linagliptin and 0.1% placebo) were noted.

The sponsor repeated the analyses of uric acid in a dataset of placebo controlled studies which the sponsor terms "MSU2". In this particular dataset, 2963 and 1539 linagliptin and placebo exposed patient had measured uric acid levels. The observed frequency of patients with uric acid elevation considered PCSA was 2.9% (N=87) and 2.6% (N=40) for linagliptin and placebo respectively.

Dr. Kwon, in her review pooled the original "SAF-2" data with additional data from study 1218.46 only and was not able to confirm either the number of reported cases or the total exposure reported by the sponsor. The addition of trial 1218.46 to SAF-2 results in a reported incident rate for increases in uric acid levels of 2.5% (71/2893) and 1.5% (22/1477) for linagliptin and placebo respectively.

Dr. Kwon issued an information request on April 10th 2012 to shed light on the discrepant results. The sponsor responded by stating that interim data from trial 1218.43 had been added to the SAF-2 + 1218.46 pooled dataset. Trial 1218.43 is a trial, currently under review at the Agency, designed to evaluate the efficacy and safety of linagliptin use in patients with moderate to severe renal insufficiency (Efficacy Supplement: #03).

Reviewer Comment: Uric acid levels can be elevated in patients with moderate to severe renal insufficiency due to loss of uricosuria. We do not feel it is appropriate to pool data from this trial with the overall trial results for the purpose of analyzing elevation in uric acid levels as it may introduce confounding. An information request was sent on April 17th 2012 asking for clarification and additional information related to elevation in uric acid levels. (b) (4)

Advisory Committee Meeting

Not applicable.

9. Pediatrics

This submission does not trigger new pediatric studies under the Pediatric Research and Equity Act (PREA) because the application does not provide for a new active ingredient, new dosage form, new route of administration, new indication or new dosing regimen.

10. Other Relevant Regulatory Issues

Review of financial disclosure form for Trial 1218.46 was performed in NDA 2012281. None of the participating investigators had a financial interest requiring disclosure.

11. Labeling

With regards to efficacy, the sponsor's proposed language and figure describing the design and main efficacy findings for Trial 1218.46 are consistent with the previously reviewed and accepted language used for Section 14 of the fixed dose combination product (Jentadueto™). Minor editing changes were made to tables describing other studies to improve clarity of the reported information (i.e., reported values for plasma glucose were rounded to whole numbers).

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval.

- Risk Benefit Assessment

In trial 1218.46, the sponsor demonstrated that glycemic control afforded by co-administration of linagliptin and metformin was superior to that afforded by administration of each drug individually (refer to Dr. Ilan Irony's NDA 201281 CDTL memorandum for details). Metformin is regarded as first-line therapy to treat type 2 diabetes patients who can tolerate and have no contraindications to the drug. In the majority of patients with type 2 diabetes, glycemic control on maximally effective doses of metforrmin worsens over time as the underlying disease process progresses. In these patients addition of linagliptin therapy to maintain glycemic control would offer a benefit.

Analyses of safety in this trial alone and in the pool of placebo controlled trial, which includes added data from trial 1218.46, did not reveal new findings of concern. In the overall dataset of placebo controlled trial, the numerical imbalances in adverse events related to myalgia and elevation in uric acid levels not favoring linagliptin are similar to those observed at the time of initial NDA filing.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There are no new safety findings from this trial that prompt the need for new postmarketing risk evaluation and management strategies.

- Recommendation for other Postmarketing Requirements and Commitments

There are no new safety findings from this trial that prompt the need for new postmarketing requirements and commitments

- Recommended Comments to Applicant

The sponsor has agreed to change Section 6.1 in accordance with PLR but asked that this be done in the context of a future supplement. A comment regarding the specific changes the Sponsor has agreed to will be communicated.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
05/08/2012

MARY H PARKS
05/10/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 201280/S-002

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201280/S-002
Priority or Standard	Standard
Submit Date(s)	July 22, 2011
Received Date(s)	July 22, 2011
PDUFA Goal Date	May 22, 2012
Division / Office	Division of Metabolism and Endocrine Products/ODE 2
Reviewer Name(s)	Hyon J. Kwon
Review Completion Date	April 17, 2012
Established Name	Linagliptin
Trade Name	Tradjenta
Therapeutic Class	Dipeptidyl-peptidase inhibitor
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Formulation(s)	Oral tablets
Dosing Regimen	5 mg daily
Indication(s)	Treatment of type 2 diabetes mellitus
Intended Population(s)	Adults with type 2 diabetes mellitus

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend the approval of this supplement, to revise the linagliptin labeling to include information on the trial 1218.46.

(b) (4)
pending an Information Request that was sent to the applicant on April 17, 2012.

1.2 Risk Benefit Assessment

Linagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, has been approved for the treatment of type 2 diabetes mellitus (T2DM) in the United States since May 2011 under NDA 201280. Data submitted in this supplement, trial 1218.46, provide an update to the overall risk benefit assessment for linagliptin. Trial 1218.46 showed benefit of coadministration of linagliptin and metformin, by demonstrating a statistically and clinically meaningful reduction in HbA1c after 12 weeks of treatment with coadministration of linagliptin and metformin compared to the treatment with corresponding doses of monotherapy, without an unacceptable rate of adverse effects with the coadministration.

In the initial linagliptin submission, the pooled dataset of all placebo-controlled trials with linagliptin in T2DM subjects (SAF-2) showed that myalgia occurred in 1.8% (47/2566) of subjects treated with linagliptin compared to 1.2% (14/1183) of subjects treated with placebo. All myalgia events were non-serious and myalgia in two subjects in linagliptin arm led to study discontinuation. No cases of rhabdomyolysis were reported in SAF-2, and the review of creatinine kinase by Dr. Dunn under the initial NDA did not present any significant findings. In the subgroup of total subjects who received metformin background therapy, > 2-fold increase in the incidence of myalgia was observed, where 2.5% (15/589) of subjects treated with linagliptin compared to 0.8% (2/248) of subjects treated with placebo experienced myalgia.

When pooled safety data containing all placebo-controlled trials with linagliptin (SAF-2) was updated with safety data from trial 1218.46, , the overall frequency of myalgia regardless of background therapy was 1.7% (71/4204) in linagliptin arm compared to 1.2% (24/2023) in placebo arm, similar to the initial data. The previously noted imbalance in the overall incidence of myalgia between treatment arms in the subgroup of subjects who received metformin as a background therapy was still observed, although the difference between treatment groups was not as wide [1.9% (17/875) in linagliptin arm compared to 1.3% (7/539) in placebo arm].

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

This supplement is submitted to revise the linagliptin labeling to include information on trial 1218.46 entitled, "A Phase 3, randomized, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naive or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycemic control". The efficacy and safety of trial 1218.46 was fully reviewed under the linagliptin/metformin fixed dose combination NDA (201281), which was approved on January 30, 2012.

(b) (4)

2.1 Product Information

Linagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor, which prevents the degradation of incretin hormones such as glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). It was approved for the treatment of T2DM in the US on May 2, 2011.

2.2 Tables of Currently Available Treatments for Proposed Indications

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and the following drug therapies, either alone or in combination:

- Biguanides: metformin (i.e., Glucophage)
- Sulfonylureas: glyburide (Micronase), glipizide (Glucotrol), glimepiride (Amaryl), chlorpropamide (Diabinese), tolazamide (Tolinase)
- Insulin
- GLP-1 agonist: exenatide (Byetta), liraglutide (Victoza)
- Thiazolidinediones (TZDs): rosiglitazone (Avandia), pioglitazone (Actos)
- Dipeptidyl peptidase 4 (DPP-4) inhibitor: sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta)
- Meglitinides: repaglinide (Prandin), nateglinide (Starlix)
- α-Glucosidase inhibitor: acarbose (Precose), miglitol (Glyset)
- Pramlintide (Symlin)
- Dopamine agonist: bromocriptine mesylate (Cycloset)
- Bile acid sequestrants: colesevelam (WelChol)
- Various fixed dose combinations of oral therapies (i.e., Jentadueto, Janumet, ActoPlus Met, Kombiglyze XR)

2.3 Availability of Proposed Active Ingredient in the United States

Linagliptin was approved for the treatment of T2DM in the US since May 2, 2011 in 5 mg daily dose.

2.4 Important Safety Issues With Consideration to Related Drugs

Labeled safety concerns with linagliptin include:

- Risk of hypoglycemia when used with an insulin secretagogue [e.g. sulfonylurea (SU)]
- Pancreatitis
- Nasopharyngitis
- Hypersensitivity reactions

2.5 Summary of Presubmission Regulatory Activity Related to Submission

None.

2.6 Other Relevant Background Information

An Information Request was sent on April 17, 2012, with the response pending at the time of writing this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality submission was acceptable. The submission was organized and information was not difficult to find.

(b) (4)

3.2 Compliance with Good Clinical Practices

Trial 1218.46 was reviewed in NDA 201281, and was found to have been conducted with Good Clinical Practices.

3.3 Financial Disclosures

Financial disclosures (FDA Form 3454) for trial 1218.46 was already reviewed in NDA 201281, and none of the investigators from trial 1218.46 had any financial interest requiring disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new information related to other review disciplines was submitted with this supplement. See reviews of other disciplines for linagliptin under the original linagliptin NDA (201280).

5 Sources of Clinical Data

This supplement was submitted electronically, with the following link:
\\CDSESUB1\EVSPROD\NDA201280\201280.enx

5.1 Tables of Studies/Clinical Trials

The trials that were included in the pooled dataset (SAF-2) in the initial linagliptin NDA for assessing safety and trial 1218.46, the trial with updated safety data for SAF-2 (MSU-2) in the 4-Month Safety Update (4MSU), are listed in Table 1. See section 7.1.3 regarding details of pooling of trials in SAF-2 and MSU-2.

The applicant had also updated uric acid data with data from trial 1218.43 (study of linagliptin in T2DM with severe renal insufficiency), which is not included in Table 1 since we do not agree with the inclusion of data from trial 1218.43. This is discussed further in section 7.3, Increases in Uric Acid.

Table 1: List of Trials Included in the Pooled Dataset for the Evaluation of Safety - SAF-2 and trial 1218.46

Trial Category	Trial Number	Trial Objective	Trial Design	Test Products, Dosage	Number of Subjects	Duration
Phase 3						
Pivotal double-blind, placebo-controlled efficacy trials	1218.15	To evaluate the efficacy and safety of linagliptin 5 mg as initial combination with pioglitazone 30 mg in comparison with placebo as initial combination with pioglitazone 30 mg	Randomized, double-blind, placebo controlled, parallel group comparison in T2DM and insufficient glycemic control	Study drugs: Linagliptin 5 mg + pioglitazone 30 mg Control drug: Placebo + pioglitazone 30 mg	Total: 389 Lina 5 mg: 259 Placebo: 130	24 weeks
	1218.16	To evaluate efficacy and safety of linagliptin 5 mg in comparison with placebo as monotherapy	Randomized, double-blind, placebo-controlled, parallel group comparison in T2DM and insufficient glycemic control	Study drugs: Linagliptin 5 mg Control drug: Placebo	Total: 503 Lina 5 mg: 336 Placebo: 167	24 weeks
	1218.17	To evaluate efficacy and safety of linagliptin 5 mg in comparison with placebo as add-on therapy to metformin	Randomized, double-blind, placebo-controlled, parallel group comparison in T2DM and insufficient glycemic control despite metformin	Study drugs: Linagliptin 5 mg Control drug: Placebo	Total: 701 Lina 5 mg: 524 Placebo: 177	24 weeks
	1218.18	To evaluate efficacy and safety of linagliptin 5 mg in comparison with placebo as add-on therapy to metformin + SU	Randomized, double-blind, placebo-controlled, parallel group comparison in T2DM and insufficient glycemic control despite metformin + SU	Study drugs: Linagliptin 5 mg Control drug: Placebo	Total: 1058 Lina 5 mg: 793 Placebo: 265	24 weeks

Additional double-blind, placebo-controlled efficacy trials	1218.35	To evaluate efficacy and safety of linagliptin 5 mg in comparison with placebo as add-on therapy to SU	Randomized, double-blind, placebo-controlled, parallel group comparison in T2DM and insufficient glycemic control despite SU	Study drugs: Linagliptin 5 mg Control drug: Placebo	Total: 245 Lina 5 mg: 161 Placebo: 84	18 weeks
	1218.50	Phase 1: To evaluate efficacy and safety of linagliptin 5 mg in comparison to placebo in patients for whom metformin therapy is inappropriate Phase 2: To investigate safety over 34 weeks in comparison with SU	Randomized, double-blind, placebo-controlled followed by active-controlled, parallel group comparison in T2DM and insufficient glycemic control for whom metformin therapy is inappropriate	Study drugs: Linagliptin 5 mg Control drug: Phase 1: Placebo Phase 2: Glimepiride 1, 2, 3, or 4 mg	Total: 227 Lina 5 mg: 151 Placebo: 76	Phase 1: 18 weeks Phase 2: 34 weeks
Double-blind, efficacy trials with more than one linagliptin dose level	1218.23	To evaluate efficacy and safety of linagliptin 5 mg and 10 mg in comparison with placebo (after 12 weeks) and in comparison with voglibose (after 26 weeks)	Randomized, double-blind, placebo-controlled, voglibose-referenced, parallel group comparison in Japanese T2DM and insufficient glycemic control	Study drugs: Linagliptin 5 mg and 10 mg Control drug: Placebo Voglibose 0.2 mg	Total: 562 Lina 5 mg: 159 Lina 10 mg: 160 Placebo: 80 Voglibose: 162	12 week placebo control, followed by 14 week active control
Phase 2						
Double-blind, efficacy trials with more than one linagliptin dose level	1218.5	To investigate efficacy and safety of linagliptin 5 mg in comparison with placebo; to explore the efficacy of metformin in comparison with placebo for sensitivity analysis	Randomized, double-blind, placebo-controlled, parallel group comparison in T2DM and insufficient glycemic control; additional open-label arm (active comparator: metformin)	Study drugs: Linagliptin 0.5 mg, 2.5 mg, 5 mg Control drug: Placebo Open-label metformin	Total: 302 Lina 0.5 mg: 58 Lina 2.5 mg: 57 Lina 5 mg: 55 Placebo: 67 Metformin: 65	12 weeks
	1218.6	To investigate efficacy and safety of 3 linagliptin doses in comparison with placebo; to explore the efficacy of glimepiride in comparison with placebo for sensitivity analysis	Randomized, double-blind, placebo-controlled, parallel group comparison in T2DM and insufficient glycemic control despite metformin; additional open-label arm (active comparator: glimepiride)	Study drugs: Linagliptin 1 mg, 5 mg, 10 mg Control drug: Placebo Open-label glimepiride	Total: 3343 Lina 1 mg: 65 Lina 5 mg: 66 Lina 10 mg: 66 Placebo: 71 Glimepiride: 65	12 weeks

	1218.37	To compare the effect of linagliptin 5 mg and sitagliptin 100 mg on 24-h glucose control with placebo and with each other	Randomized, double-blind, double-dummy, placebo-controlled, parallel group comparison in T2DM	Study drugs: Linagliptin 5 mg Sitagliptin 100 mg Control drug: Matching placebo for linagliptin and sitagliptin	Total: 121 Lina 5 mg: 40 Sitagliptin: 41 Placebo: 40	4 weeks
Phase 1						
PK in T2DM	1218.2	To investigate safety, tolerability, PK, and PD of linagliptin after oral administration of multiple rising doses	Randomized, placebo-controlled, double-blind within dose groups, multiple rising doses, in male patients with T2DM	Study drugs: Linagliptin solution 1 mg, 2.5 mg, 5 mg, 10 mg Control drug: Placebo solution	Total: 48 Lina 1 mg: 9 Lina 2.5 mg: 9 Lina 5 mg: 9 Lina 10 mg: 9 Placebo: 12	12 days
	1218.3	To investigate safety, tolerability, PK, and PD of linagliptin during 4 week treatment	Randomized, placebo-controlled, double-blind within dose group, multiple dose study in male and postmenopausal female patients with T2DM	Study drugs: Linagliptin solution 2.5 mg, 5 mg, 10 mg Control drug: Placebo solution	Total: 77 Lina 2.5 mg: 26 Lina 5 mg: 16 Lina 10 mg: 19 Placebo: 16	28 days
Reported at 4 Month Safety Update, Phase 3						
Linagliptin/ Metformin Combination Trial	1218.46	To evaluate the efficacy and safety of twice daily (BID) administration of lina 2.5 mg + metformin 500 mg, lina 2.5 + metformin 1000 mg, compared to the individual components of metformin 500 mg or 1000 mg BID and lina 5 mg daily	Randomized, double-blind, placebo controlled, factorial design	Study drugs: Lina 2.5 mg + metformin 500 mg BID Lina 2.5 mg + metformin 1000 mg BID Control drug: Lina 5 mg daily Metformin 500 mg BID Metformin 1000 mg BID	Total: 791 Lina 2.5 +metformin 500: 143 Lina 2.5 +metformin 1000: 143 Lina 5 mg: 142 Metformin 500: 144 Metformin 1000: 147 Placebo: 72	24 weeks

Source: 4 Month Safety Update of NDA 201280, Table 1.1:1

5.2 Review Strategy

There are no new data to review for this supplement with regard to trial 1218.46. I will refer to the Clinical Review under NDA 201281 for discussion of efficacy and safety for trial 1218.46.

This review will focus on the updated safety data related to reassessment of myalgia and increases in uric acid with linagliptin with data from trial 1218.46. Therefore, the review template of section 7, Review of Safety has been adjusted to specifically discuss myalgia and increases in uric acid.

5.3 Discussion of Individual Studies/Clinical Trials

See the Clinical Review under NDA 201281 for discussion of trial 1218.46.

6 Review of Efficacy

Efficacy Summary

The efficacy of trial 1218.46 was fully reviewed in the linagliptin/metformin fixed dose combination NDA (201281) - see the Clinical Review under NDA 201281 for full details.

In summary, trial 1218.46 was a multinational, multicenter, Phase 3, randomized, double-blind, placebo-controlled trial to compare the efficacy and safety of twice daily (BID) coadministration of linagliptin 2.5 mg+metformin 500 mg, linagliptin 2.5 mg+metformin 1000 mg, to the individual components of metformin 500 mg BID, metformin 1000 mg BID, and linagliptin 5 mg daily. A total of 791 subjects were randomized 1:2 ratio of placebo to all the other active treatment arms.

The primary endpoint was the change in HbA1c at week 24, and the results in the FAS demonstrated a clinically meaningful reduction with combination therapies when compared to the treatment with corresponding doses of monotherapy:

- The coadministration of linagliptin 2.5 mg and metformin 1000 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.5% [SE=0.11], $p<0.001$) when compared to metformin 1000 mg BID
- The coadministration of linagliptin 2.5 mg and metformin 1000 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -1.1% [SE=0.11], $p<0.0001$) when compared to linagliptin 5 mg daily
- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.6% [SE=0.11], $p<0.001$) when compared to metformin 500 mg BID
- The coadministration of linagliptin 2.5 mg and metformin 500 mg BID resulted in a significant improvement in HbA1c (mean treatment difference, -0.8% [SE=0.11], $p<0.0001$) when compared to linagliptin 5 mg daily

7 Review of Safety

Safety Summary

The safety of trial 1218.46 was reviewed in NDA 201281 - see the Clinical Review under NDA 201281 for full details.

The applicant updated the pooled dataset of all placebo-controlled trials with linagliptin in T2DM subjects (SAF-2), which was used for identifying possible adverse events that may be associated with linagliptin in the initial NDA submission, with data from trial 1218.46.

Myalgia

In SAF-2 of the initial linagliptin submission, the overall incidence of myalgia was 1.8% (47/2566) in subjects treated with linagliptin compared to 1.2% (14/1183) in subjects treated with placebo. Myalgia events were all non-serious and myalgia in two subjects in linagliptin arm led to study discontinuation. No cases of rhabdomyolysis were reported in SAF-2, and the review of creatinine kinase by Dr. Dunn under the initial NDA did not present any significant findings. In the subgroup of total subjects by antidiabetic background therapy, > 2-fold increase in the incidence of myalgia was observed when linagliptin was used as an add-on treatment to metformin, where 2.5% (15/589) of subjects treated with linagliptin compared to 0.8% (2/248) of subjects treated with placebo experienced myalgia.

In the updated safety data of SAF-2 with data from trial 1218.46, the overall frequency of myalgia was similar to SAF-2, 1.7% (n=71/4204) in subjects treated with linagliptin compared to 1.2% (24/2023) in subjects treated with placebo. In the subgroup of subjects on metformin background therapy, the imbalance in the incidence of myalgia was still observed in the updated safety data: 1.9% (17/875) of subjects treated with linagliptin compared to 1.3% (7/539) of subjects treated with placebo experienced myalgia.

Increases in Uric Acid

In the initial submission, the analysis of SAF-2 showed that the increases in Potentially Clinically Significant Abnormalities (PCSA) of uric acid occurred more frequently in the linagliptin treatment arm and ≥ 1% more than in placebo. The incidence of subjects with increases in PCSA of uric acid was 2.7% (68/2963) in subjects treated with linagliptin compared to 1.3% (15/1539) in subjects treated with placebo. There was no clinically significant increase in adverse events that may be associated with increases in uric acid such as gout (0.2% in both treatment arm) or kidney stones (0.3% linagliptin and 0.1% placebo).

In the updated safety data of SAF-2 with data from trial 1218.46, the incidence of increases in PCSA of uric acid was 2.5% (71/2893) in subjects treated with linagliptin and 1.5% (22/1477) in subjects treated with placebo.

7.1 Methods

SAF-2, which contained all the placebo-controlled trials with linagliptin in T2DM subjects, is one of the main pooled dataset that was analyzed for identifying possible adverse events that may be associated with linagliptin in NDA 201280. The applicant updated SAF-2 in the 4MSU with data from trial 1218.46. See the details of pooled data used in the safety evaluation of linagliptin in section 7.1.3, Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.

In this review, I will focus on the updated pooled safety data of SAF-2 in reassessing myalgia and increases in uric acid reported with linagliptin.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See the list of clinical trials used to evaluate the safety of linagliptin in section 7.1.3, Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence. For details regarding each clinical trial, see section 5.1, Table of Studies/Clinical Trials, which lists all the trials that were included in the pooled dataset for assessing myalgia and increases in uric acid.

7.1.2 Categorization of Adverse Events

Myalgia was considered as a medical concept by grouping the following MedDRA preferred terms (PT): muscle tightness, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, and myalgia.

Potential Clinically Significant Abnormalities (PCSA) of uric acid was defined as a laboratory value above the upper limit of normal during treatment, and the reference range for uric acid was 2.4 to 6.5 mg/dL.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

SAF-2 is one of the main pooled dataset that was analyzed for identifying possible adverse events that may be associated with linagliptin in NDA 201280, and contained all the placebo-controlled trials with linagliptin in T2DM subjects. All the trials that were included in SAF-2 are listed in Table 2.

Table 2: Grouping of Studies for SAF-2, NDA 201280

								Patient numbers N (%)		
Safety grouping	Objective	Trial characteristics	Studies	Phase	Treatment duration	Doses	Patients / Healthy subjects	Total (random.)	Linagliptin (treated)	Linagliptin 5 mg (treated)
SAF-2	Safety in patients with T2DM on linagliptin 5 mg	Placebo-controlled trials with lingliptin 5 mg in patients with T2DM	1218.2	I	12 days	1, 2.5, 5, 10 mg	P	48 (100.0)	35 (72.9)	8 (16.7)
			1218.3	I	28 days	2.5, 5, 10 mg	P	77 (100.0)	59 (76.6)	15 (19.5)
			1218.5[o]	II	12 weeks	0.5, 2.5, 5 mg	P	302 (100.0)	170 (56.3)	55 (18.2)
			1218.6[p]	II	12 weeks	1, 5, 10 mg	P	333 (100.0)	197 (59.2)	66 (19.8)
			1218.15	III	24 weeks	5 mg	P	389 (100.0)	259 (66.6)	259 (66.6)
			1218.16	III	24 weeks	5 mg	P	503 (100.0)	336 (66.8)	336 (66.8)
			1218.17	III	24 weeks	5 mg	P	701 (100.0)	523 (74.6)	523 (74.6)
			1218.18	III	24 weeks	5 mg	P	1058 (100.0)	792 (74.9)	792 (74.9)
			1218.23[q]	III	52 weeks[b]	5, 10 mg	P (Japan)	561 (100.0)	319 (56.9)	159 (28.3)
			1218.35	III	18 weeks	5 mg	P	245 (100.0)	161 (65.7)	161 (65.7)
			1218.37	II	4 weeks	5 mg	P	121 (100.0)	40 (33.1)	40 (33.1)
			1218.50	III	18 weeks[e]	5 mg	P	227 (100.0)	151 (66.5)	151 (66.5)
Total patient numbers in SAF-2, N (%)								4565 (100.0)	3042 (66.6)	2565 (56.2)

Source: NDA 201280, SCS, Table 1.1.3:1, page 28

In the 4MSU of NDA 201280, the updated safety information for SAF-2 came from trial 1218.46 (MSU-2). Trial 1218.46 had the following treatment arms: linagliptin 2.5 mg + metformin 500 mg BID, linagliptin 2.5 mg + metformin 1000 mg BID, linagliptin 5 mg daily, metformin 500 mg BID, metformin 1000 mg BID, and placebo.

In the update, the applicant reassessed the safety of myalgia by forming two pooled dataset based on background therapy: 1) linagliptin monotherapy (MSU-2A), and 2) linagliptin with metformin background therapy (MSU-2B). See the overview of pooled datasets for MSU-2A and MSU-2B in Table 3. It should be noted that trials 1218.15, 1218.18, and 1218.35 that were in SAF-2 pooled dataset were not included either in MSU-2A or MSU-2B, since these trials had studied linagliptin in those with background therapy of pioglitazone, metformin and SU, and SU respectively.

Table 3: Studies pooled for MSU-2A and MSU-2B in the 4 Month Safety Update, NDA 201280

						Patient numbers N (%)		
Safety grouping	Objective	Trial characteristics	Studies	Phase	Doses	Placebo (treated)	Linagliptin 5 mg (treated)	Total (random.)
MSU-2A	Safety in patients with T2DM on linagliptin 5 mg monotherapy	Placebo-controlled trials with linagliptin 5 mg monotherapy in patients with T2DM	1218.2	I	1, 2.5, 5, 10 mg	12 (2.3)	8 (0.9)	20 (1.4)
			1218.3	I	2.5, 5, 10 mg	16 (3.0)	16 (1.8)	32 (2.2)
			1218.5	II	0.5, 2.5, 5 mg	67 (12.6)	55 (6.1)	122 (8.5)
			1218.16	III	5 mg	167 (31.5)	336 (37.0)	503 (35.0)
			1218.23	III	5, 10 mg	80 (15.1)	159 (17.5)	239 (16.6)
			1218.37	II	5 mg	40 (7.5)	40 (4.4)	80 (5.6)
			1218.46[c]	III	5 mg	72 (13.6)	142 (15.7)	214 (14.9)
			1218.50	III	5 mg	76 (14.3)	151 (16.6)	227 (15.8)
Total patient numbers in MSU-2A, N (%)						530 (100)	907(100)	1437 (100)
MSU-2B	Safety in patients with T2DM on linagliptin 5 mg with metformin background	Placebo-controlled trials with linagliptin 5 mg with metformin background in patients with T2DM	1218.6	II	1, 5, 10 mg	71 (13.2)	66 (7.5)	137 (9.7)
			1218.17	III	5 mg	177 (32.8)	523 (59.8)	700 (49.5)
			1218.46[d]	III	5 mg	291 (54.0)	286 (32.7)	577 (40.8)
Total patient numbers in MSU-2B, N (%)						539 (100.0)	875 (100.0)	1414 (100.0)

c Only patients on Placebo and Linagliptin 5 mg qd in Trial 1218.46 are included in MSU2A
d Patients on Placebo and Linagliptin 5 mg qd in 1218.46 are not included in MSU2B because metformin was not part of the treatment regimen. Treatment group 'placebo' includes patients treated with metformin monotherapy in 1218.46.
Source data: MSU-2A [Appendix 7.1, Table 1.2.2.1.1], MSU-2B [Appendix 7.1, Table 1.2.2.2.1]

Source: NDA 201280, 4 Month Safety Update, Table 1.1.3:1, page 39

As noted in Table 3, subjects randomized to placebo or linagliptin 5 mg in trial 1218.46 were pooled with previous linagliptin monotherapy dataset where linagliptin monotherapy is compared to the placebo (with no background therapy). Subjects randomized to the linagliptin and metformin combination and metformin therapy in trial 1218.46 were pooled with previous linagliptin with metformin background therapy dataset where linagliptin + metformin group is compared to placebo + metformin group.

7.2 Myalgia

The overall frequency of myalgia in SAF-2 in the initial submission

In SAF, the pooled safety dataset of all placebo-controlled trials with linagliptin, 2566 subjects received linagliptin 5 mg and 1183 subjects received placebo, and myalgia occurred in 1.8% (47/2566) of subjects treated with linagliptin compared to 1.2% (14/1183) of subjects treated with placebo. The overall treatment exposure was 1041 patient-years in linagliptin arm and 434 patient-years in placebo arm, and the rate of myalgia was 4.51/100patient-years and 3.23/100patient-years in linagliptin and placebo arm respectively. None of these myalgia events were serious, but myalgia events in two subjects in linagliptin arm led to study discontinuation.

No cases of rhabdomyolysis were reported in SAF-2. In the Laboratory section (7.4.2) of the Clinical Review under NDA 201280, Dr. Dunn noted a higher transitions from normal to high values in the linagliptin group in creatinine kinase (CK) (5.7% linagliptin compared to 4.5% placebo), but she determined that this trend in CK was due to an outlier effect, rather than an overall increase in CK levels over time. In the Common Adverse Events section (7.4.1), Dr. Dunn noted an increase in the proportion of subjects reporting Musculoskeletal Conditions System Organ Class adverse events in the linagliptin treatment arm (10.3% in the linagliptin group compared to 8.6% in the placebo group). However, she did not detect any particular concerns or clear trends, except for noting a difference between treatment groups for asthenia (2.3% in linagliptin group versus 0.8% in placebo group, per her database calculation).

The frequency of myalgia for each trial included in SAF-2 is shown in Table 4.

Table 4: Frequency [% (N)] of Subjects with Adverse Events of Myalgia in Each Trial (Treated Set, SAF-2)

Trial (background therapy)	Treatment Arm	
	Linagliptin 5 mg	Placebo
1218.05 (none)	0 (0/55)	3% (2/67)
1218.06 (metformin)	4.5% (3/66)	1.4% (1/71)
1218.15 (pioglitazone)	0.4% (1/259)	0.8% (1/130)
1218.16 (none)	1.2% (4/336)	0.6% (1/167)
1218.17 (metformin)	2.3% (12/523)	0.6% (1/177)
1218.18 (metformin+SU)	1.9% (15/792)	0.8% (2/263)
1218.23 (none)	2.5% (4/159)	2.5% (2/80)
1218.35 (SU)	1.9% (3/161)	1.2% (1/84)
1218.50 (none)	3.3% (5/151)	3.9% (3/76)
Total	1.8% (47/2566)	1.2% (14/1183)

The frequency of myalgia by background therapy in the initial submission

The applicant also assessed the side effect profile of linagliptin as add-on treatment to background therapies such as metformin, metformin+SU, SU, and pioglitazone by analyzing subgroup of total subjects by antidiabetic background therapy.

In the subgroup of subjects who received metformin as a background therapy, myalgia occurred in 2.5% (n=15) of 589 subjects treated with linagliptin compared to 0.8% (n=2) of 248 subjects treated with placebo. In trials with metformin and SU as background therapy, 1.9% (n=15) of 792 subjects treated with linagliptin compared to 0.8% (n=2) of 263 subjects treated with placebo experienced myalgia. In trials with SU as background therapy, 1.9% (n=3) of 161 subjects treated with linagliptin compared to 1.2% (n=1) of 84 subjects treated with placebo experienced myalgia. A difference in the incidence of myalgia between treatment arms was not observed in the subgroups where subjects did not receive any background therapy or received pioglitazone as a background therapy. This data is summarized in Table 5.

Table 5: Frequency [%(N)] of Subjects with Adverse Events of Myalgia by Background Therapy (Treated Set, SAF-2)

Background therapy	Linagliptin 5 mg	Placebo
Metformin	2.5% (15/589)	0.8% (2/248)
Metformin + SU	1.9% (15/792)	0.8% (2/263)
SU	1.9% (3/161)	1.2% (1/84)
Pioglitazone	0.4% (1/259)	0.8% (1/130)
None	1.7% (13/701)	1.7% (8/390)

Source: NDA 201280, SCS Appendix and ISS, Module 5.3.5.3, Table 5.2.2.10.2

Through this subgroup analysis, myalgia was identified as a possible side effect when linagliptin was given as an add-on treatment to metformin, since the difference between the treatment arms (2.5% versus 0.8% in the linagliptin versus placebo arm respectively) was > 2-fold.

Reviewer's comment: As there is no drug-drug interaction between linagliptin and metformin, it is unclear why there is an increased incidence of myalgia when linagliptin is given with metformin as background therapy.

Updated frequency of myalgia in the 4-month safety update

In the 4-month safety update (4MSU) of NDA 201280, the updated safety information for SAF-2 came from trial 1218.46. As discussed in section 7.1.3, the applicant assessed the safety by forming two pooled dataset based on background therapy: 1) linagliptin monotherapy (MSU-2A), and 2) linagliptin with metformin background therapy (MSU-2B). The updated dataset of linagliptin with metformin background therapy from trial 1218.46 (MSU-2B) represents more than 40% larger database for linagliptin+metformin arm and more than 2-fold larger database for placebo+metformin arm.

The updated placebo-controlled linagliptin monotherapy dataset without any background therapy (MSU-2A) included 907 subjects treated with linagliptin and 530 subjects treated with placebo. Myalgia was observed in 1.8% (n=16) of subjects treated with linagliptin compared to 1.7% (n=9) of subjects treated with placebo. This compares with 1.7% in linagliptin arm compared to 1.7% in placebo arm in the initial SAF-2 dataset of linagliptin monotherapy without any background therapy (see Table 5 with background therapy of 'none').

The updated placebo-controlled linagliptin trials with metformin as a background therapy (MSU-2B) included 875 subjects treated with linagliptin and 539 subjects treated with placebo. Myalgia was observed in 1.9% (n=17) of subjects treated with linagliptin compared to 1.3% (n=7) of subjects treated with placebo. This compares with 2.5% in linagliptin arm compared to 0.8% in placebo arm in the initial SAF-2 dataset of linagliptin with metformin as a background therapy (see Table 5 with background therapy of 'metformin').

As noted previously, trials 1218.15, 1218.18, and 1218.35 that were in the SAF-2 pooled dataset were not included either in MSU-2A or MSU-2B. Thus, I calculated the overall frequency of linagliptin compared to placebo treatment arm in all the placebo-controlled trials with linagliptin in T2DM subjects, regardless of background therapy, by pooling the safety data from trial 1218.46 to SAF-2 (without forming two groups based on the background therapy as the sponsor had done). Since trial 1218.46 is also a placebo-controlled trial with linagliptin, and is the main source of safety update in this supplement, pooling of trial 1218.46 data and SAF-2 would reassess the overall frequency of myalgia with linagliptin regardless of background therapy. Of 4204 subjects treated with linagliptin and 2023 subjects treated with placebo in pooled dataset of SAF-2 and trial 1218.46, 1.7% (n=71) and 1.2% (n=24) experienced myalgia respectively.

Reviewer's comment: In the overall pooled safety data of the initial submission (SAF-2), there was a slight imbalance in the incidence of myalgia between linagliptin and placebo treatment arm [1.8% (47/2566) linagliptin versus 1.2% (14/1183) placebo]. In an additional analysis done by background therapy, > 2-fold increase in the incidence of myalgia in the linagliptin arm compared to the placebo arm was observed with metformin as the background therapy [2.5% (15/589) linagliptin versus 0.8% (2/248) placebo].

In the updated safety data of SAF-2 with data from trial 1218.46 , the slight imbalance in the incidence of myalgia between treatment arms was similarly observed in the overall population [1.7% (71/4204) linagliptin versus 1.2% (24/2023) placebo]. In the subgroup of subjects with metformin as the background therapy, the previously noted imbalance in the overall incidence of myalgia between treatment arms, although improved, still existed [1.9% (17/875) linagliptin versus 1.3% (7/539) placebo]. (b) (4)

7.3 Increases in Uric Acid

Frequency of 'increases in uric acid' in the initial submission

In the initial linagliptin submission (NDA 201280), an increase in Potential Clinically Significant Abnormalities (PCSA) of uric acid occurred more frequently in the linagliptin treatment arm and ≥ 1% more than in placebo. Similar to myalgia, this was based on the data from the largest available placebo-controlled pooled data (SAF-2), where uric acid measurements were available in 2489 subjects treated with linagliptin and 1140 subjects treated with placebo. The incidence of subjects with increases in PCSA of uric acid was 2.7% (68/2489) of subjects treated with linagliptin compared to 1.3% (15/1140) of subjects treated with placebo.

In addition, transitions from baseline normal to high values on treatment occurred more in the linagliptin group compared to the placebo group, 5.5% versus 3.4% respectively, as shown in Table 6. In the Clinical Review of NDA 201280, Dr. Dunn's review of uric acid found that the trend in uric acid appeared to be due to outliers and not from an overall increase in the uric acid level for the treated patients.

Table 6: Frequency of Subjects [N(%)] categorized by reference range at baseline and last value, minimum value, and maximum value on treatment (Treated Set, SAF-2)

Treatment/ Baseline	Last Value on Treatment			Min Post Baseline		Max Post Baseline		Total
	Low	Normal	High	Low	Normal,High	Low,Normal	High	
Placebo								
Low	11 (1.0)	18 (1.6)	0	16 (1.4)	13 (1.1)	29 (2.5)	0	29 (2.5)
Normal	16 (1.4)	929 (81.5)	39 (3.4)	26 (2.3)	958 (84.0)	926 (81.2)	58 (5.1)	984 (86.3)
High	0	61 (5.4)	66 (5.8)	0	127 (11.1)	41 (3.6)	86 (7.5)	127 (11.1)
Total	27 (2.4)	1008 (88.4)	105 (9.2)	42 (3.7)	1098 (96.3)	996 (87.4)	144 (12.6)	1140 (100.0)
Lina 5mg								
Low	23 (0.9)	30 (1.2)	0	30 (1.2)	23 (0.9)	53 (2.1)	0	53 (2.1)
Normal	16 (0.6)	2011 (80.8)	136 (5.5)	32 (1.3)	2131 (85.7)	1962 (78.9)	201 (8.1)	2163 (86.9)
High	0	96 (3.9)	176 (7.1)	0	272 (10.9)	53 (2.1)	219 (8.8)	272 (10.9)
Total	39 (1.6)	2137 (85.9)	312 (12.5)	62 (2.5)	2426 (97.5)	2068 (83.1)	420 (16.9)	2488 (100.0)

Source: NDA 201280, Module 5.3.5.3. SCS Appendix and ISS, Table 6.2.2.1

Clinical adverse events that may be associated with increases in uric acid such as gout and kidney stones occurred at low incidences. The incidence of gout was comparable in both treatment arms [0.2% in both linagliptin (5/2566) and placebo arm (2/1183)]. Nephrolithiasis occurred in 0.3% (7/2566) and 0.1% (1/1183) of linagliptin and placebo arm respectively.

From twelve trials that were included in SAF-2, six trials showed a higher incidence of increases in PCSA of uric acid in the linagliptin treatment arm compared to placebo, and additional analysis with uric acid in these trials are summarized in Table 7. Consistent with the overall SAF-2, the proportion of subjects with transitions from baseline low/normal to high values on treatment occurred more in the linagliptin group compared to the placebo group in these trials. The overall mean change in the uric acid level from baseline in the linagliptin treatment arm was slightly increased (range 0.2 to 0.5 mg/dL), whereas a slight decrease was observed in the placebo arm (range -0.3 to 0 mg/dL).

Table 7: Trials in SAF-2 Reporting a Higher Frequency of Increases in PCSA of Uric Acid in the Linagliptin Treatment Arm

Trial number	Linagliptin			Placebo		
	Number (%) of subjects with PCSA of increase in uric acid	Transitions from baseline low, normal to high on treatment	Mean change in uric acid level from baseline (mg/dL)	Number (%) of subjects with PCSA of increase in uric acid	Transitions from baseline low, normal to high on treatment	Mean change in uric acid level from baseline (mg/dL)
1218.5	2 (3.8%)	4.1%	0.2	0	3.8%	0
1218.6	4 (6.3%)	11.3%	0.3	2 (2.8%)	7.8%	-0.2
1218.16	8 (2.4%)	6.8%	0	0	2.1%	-0.3
1218.18	25 (3.2%)	4.9%	0.2	4 (1.5%)	3.1%	-0.2
1218.35	8 (5.1%)	9%	0.3	1 (1.2%)	1.4%	0
1218.50	6 (4.7%)	14.8%	0.5	0	2.2%	-0.1

PCSA= Potential Clinically Significant Abnormalities

Updated frequency of 'increases in uric acid' in the 4-month safety update

The applicant reported an updated frequency of increases in PCSA of uric acid as 2.9% (87/2963) in linagliptin arm and 2.6% (40/1539) in placebo arm in their response on September 21, 2011 to our Information Request (IR). Although they stated that this updated frequency came from trial 1218.46, the updated frequency of PCSA in uric acid with data from trial 1218.46 corresponds to 2.5% (71/2893) in subjects treated with linagliptin and 1.5% (22/1477) in subjects treated with placebo. Another IR was sent on April 10, 2012 to clarify the overall frequency, and the applicant responded on April 13, 2012 stating that this discrepancy is due to additional subjects with PCSA of uric acid from trial 1218.43 based on data from a snapshot taken on April 13, 2010. Per applicant, data from trial 1218.43 included an additional 16 subjects to the linagliptin arm and 18 subjects to the placebo arm, as presented in Table 8. Document supporting this has not been submitted yet.

Table 8: Updated Frequency of Increases in Uric Acid by the Applicant

Source	Linagliptin	Placebo
Initial PCSA based on SAF-2	68	15
1218.46 final CTR	3	7
1218.43 snapshot	16	18
Total Update	87 (2.9%)	40 (2.6%)

Source: Applicant's response to IR on April 13, 2012

Reviewer's comment: The applicant included data from trial 1218.43 in updating increases in uric acid. However, trial 1218.43 was studied in T2DM subjects with severe renal insufficiency, and I do not agree that the results of this study should be pooled with SAF-2 and trial 1218.46, as subjects in trial 1218.43 have elevated uric acid levels at baseline due

to renal insufficiency and could confound the overall results. In addition, this data is based on an interim analysis, and the final study reports or data have not been submitted for review yet.

Therefore, I recommend updating SAF-2 data only with data from trial 1218.46; this include 2893 subjects treated with linagliptin and 1477 subjects treated with placebo. The frequency of PCSA in uric acid was 2.5% (71/2893) in subjects treated with linagliptin and 1.5% (22/1477) in subjects treated with placebo. With this update, the imbalance in the PCSA of increased uric acid between treatment arms still exists at ≥1%. (b) (4) **recommend updating the statement with the frequency observed in the updated safety dataset, 2.5% in subjects treated with linagliptin and 1.5% in subjects treated with placebo.**

(b) (4)

8 Postmarket Experience

Not applicable, since the safety update is for the adverse reactions from clinical trials.

9 Labeling Recommendations

I have the following labeling recommendations:

- I recommend updating the linagliptin labeling with efficacy and safety data from trial 1218.46 in sections 6, Adverse Reactions, 6.1 Clinical Trials Experience, and 14, Clinical Studies.
- (b) (4)

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/s/

HYON J KWON
04/17/2012

JEAN-MARC P GUETTIER
04/17/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Filing Meeting: September 6, 2011
NDA 201280/S-02
Drug: Trandjenta™ (linagliptin)
Sponsor: Boehringer Ingelheim (BI)
Clinical Reviewer: Hyon J. Kwon, PharmD, MPH
Date received: July 22, 2011
PDUFA date: May 22, 2012

Assessment:

From the clinical standpoint, the NDA is fileable.

Background:

Linagliptin was approved on May 2, 2011. Currently, linagliptin/metformin fixed dose combination NDA (201281) is under review with the PDUFA goal date of November 19, 2011.

This supplement is to add the clinical information from trial 1218.46 to the linagliptin labeling. Trial 1218.46 is the pivotal factorial trial supporting the linagliptin/metformin fixed dose combination NDA 201281.

(b) (4)

Site Inspections:

None, as the site inspections for trial 1218.46 is being conducted under NDA 201281.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201280 **Applicant: Boehringer Ingelheim** **Stamp Date: July 22, 2011**

Drug Name: Linagliptin **NDA/BLA Type: supplement**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.,* Module 2 summaries)?	x			No Module 2 summary
9.	Has the applicant submitted the integrated summary of safety (ISS)?			x	single study efficacy supplement
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	
11.	Has the applicant submitted a benefit-risk analysis for the product?			x	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			x	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1			x	single study supplement

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	single study supplement
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			AE coded using version 13.0 of MedDRA in trial 1218.46
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	None requested by clinical
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	None requested
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Clinical Comments for the 74-day letter:

- (b) (4)

Hyon J. Kwon, PharmD, MPH	September 6, 2011
Reviewing Medical Officer	Date
Ilan Irony, MD	September 6, 2011
Clinical Team Leader	Date

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/s/

HYON J KWON
09/06/2011

ILAN IRONY
09/07/2011
I concur with Dr. Kwon's recommendation for filing the supplement and with the comment to convey to the applicant.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 201280/S-002

PHARMACOLOGY REVIEW(S)

Memorandum

PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

Date:	19 September, 2011
NDA #	201280 / S-02 Efficacy Supplement
Sponsor:	Boehringer Ingelheim Pharma. Inc. (BIPI)
Drug:	Tradjenta® (linagliptin)
Reviewer:	David B. Carlson, Ph.D.

Summary: Boehringer Ingelheim submitted an efficacy supplement to NDA 201280 for linagliptin tablets (Tradjenta®). The supplement consists of a single clinical study report for trial 1218.46, a phase III study of twice daily combination treatment of linagliptin (2.5 mg) and metformin (500 or 1000 mg) compared to individual drug treatments. No pharmacology or toxicology studies were submitted to support the proposed labeling and package insert changes.

Clinical study report 1218.46 was also previously submitted under NDA 201281 to support safe use of a linagliptin plus metformin fixed dose combination (FDC) tablet. Review of pharmacology/toxicology information supporting the FDC tablet under NDA 201281 is currently ongoing. The pharmacology/toxicology recommendation with respect to the potential benefits and risks of type 2 diabetes treatment with the FDC tablet in NDA 201281 will consider the clinical results from trial 1218.46.

Conclusions: The efficacy supplement is sufficient for filing from a pharmacology/toxicology perspective. Because no new pharmacology/toxicology studies were submitted and the clinical study report is under review for the FDC tablet in NDA 201281, **no further pharmacology/toxicology review of trial 1218.46 under this efficacy supplement for NDA 201280 is necessary.**

Internal comments: No further pharm/tox review will be done for this efficacy supplement and we do not expect to submit any additional review memos.

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/s/

DAVID B CARLSON
09/19/2011
Pharmtox -- OK to file and NAI (no further pharmtox review required)

TODD M BOURCIER
09/21/2011
pharm/tox nai for efficacy supplement

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 201280/S-002

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 201280-S02, eCTD Sequence Number 0045
Drug Name:	Linagliptin/Metformin Hydrochloride Tablets
Indication(s):	To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date(s):	Jauly 22, 2011
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Wei Liu, Ph.D.
Concurring Reviewers:	J. Todd Sahlroot, Ph.D. (Deputy Director)
Medical Division:	Metabolism and Endocrinological Products (HFD-510, DMEP)
Clinical Team:	Hyon Kwon, M.D. Jean-Marc Guettier, M.D. (Team Leader)
Project Manager:	Raymond Chiang

Keywords: NDA review, clinical studies, factorial design

1. EXECUTIVE SUMMARY

This NDA supplement 201280/S-02 was submitted to FDA on July 22, 2011 for labeling the use of Tradjenta (linagliptin)/metformin fixed dose combination in subjects with type 2 diabetes mellitus after 24 weeks of randomized treatment. Data supporting this labeling comes from NDA 201281 Study 1218.46. Efficacy data in this study were previously reviewed by this reviewer as part of NDA 201281.

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/s/

WEI LIU
03/02/2012

JON T SAHLROOT
03/02/2012

STATISTICS FILING CHECKLIST FOR NDA/BLA

NDA Number: 201280/S02 **Applicant:** Boehringer Ingelheim **Stamp Date: 7/22/2011**

Drug Name: Linagliptin **NDA/BLA Type: New NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			For efficacy and in some trials for safety
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			LOCF method

Comment: No statistical review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR NDA/BLA

Wei Liu	**09/06/2011**
Reviewing Statistician	Date
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA

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/s/

WEI LIU
09/06/2011

JON T SAHLROOT
09/06/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 201280/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Memorandum

Memo Date:	**July 13, 2012**
Subject:	**Prior Approval Supplement – addition of efficacy information**
NDA:	**NDA 201280/S-003 Tradjenta (linagliptin)**
Sponsor	**Boehringer Ingelheim**
Indication	**as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**
Reviewer	**Immo Zdrojewski, Ph.D.**
Team Leader (acting)	**Jaya Vaidyanathan, Ph.D.**

The purpose of this memorandum is to evaluate the steady-state plasma concentration of linagliptin in renal impaired patients.

Background:
In this submission, dated 10/14/2011, the sponsor submits results from a phase III, randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study (study # 1218.43) of 5 mg linagliptin (BI 1356). Results are compared to placebo as add on therapy to pre-existing antidiabetic therapy (insulin or any combination with insulin; sulphonylurea or glinides as monotherapy; pioglitazone or any other antidiabetics, excluding only DPP-4 inhibitors other than BI 1356 over 52 weeks in type 2 diabetic patients with severe chronic renal impairment.

Under the original NDA (DARRTs date 08/27/2010, Dr. Lokesh Jain), the sponsor submitted 12-week interim data from trial 1218.43. Based on Dr. Jain's review, trough concentrations were comparable to concentrations observed in Japanese patients after a 10 mg dose of linagliptin (mean C_{trough} 8.07-8.92 μM). Please see Dr. Jain's review form more details. Additionally, Dr. Jain concluded that at doses between 1 mg to 10 mg renal elimination appears to play a minor role in overall renal disposition and that renal excretion of the parent compound appeared to be a minor pathway of elimination accounting for about 6% of the total clearance in the 5 mg dose group. Furthermore, no trend of increase in linagliptin trough concentrations with deteriorating renal function from moderate renal impairment to severe renal impairment was observed.

No dose-adjustment was recommended for subjects with renal impairment.

Results in this submission:

Of the 68 patients in the linaglitptin group, 5 patients had an estimated glomerular filtration rate (eGFR) of 30 to <60 mL/min (moderate renal impairment), 63 patients had a eGFR of 15 to <30 mL/min (severe renal impairment) and 8 patients had a eGFR of <15 mL/min (end stage renal disease) (Table 1).

Table 1 Demographic data - Treated patients

	Placebo	Linagliptin	Total
Number of patients	65 (100.0)	68 (100.0)	133 (100.0)
Gender [N (%)]			
Male	35 (53.8)	45 (66.2)	80 (60.2)
Race, N (%)			
Asian	11 (16.9)	8 (11.8)	19 (14.3)
Black/African Amer.	7 (10.8)	6 (8.8)	13 (9.8)
Hawaiian/Pacif. Isle	2 (3.1)	1 (1.5)	3 (2.3)
White	45 (69.2)	53 (77.9)	98 (73.7)
Ethnicity, N (%)			
Not Hispanic/Latino	61 (93.8)	64 (94.1)	125 (94.0)
Hispanic/Latino	4 (6.2)	4 (5.9)	8 (6.0)
Age [years]			
Mean (SD)	64.9 (9.6)	64.0 (10.9)	64.4 (10.3)
Age groups [years], N (%)			
<65	30 (46.2)	29 (42.6)	59 (44.4)
65 to 74	25 (38.5)	31 (45.6)	56 (42.1)
≥75	10 (15.4)	8 (11.8)	18 (13.5)
Baseline weight [kg]			
Mean (SD)	85.7 (17.6)	89.9 (19.0)	87.8 (18.3)
Baseline weight, categorical [kg], N (%)			
≤70	15 (23.1)	9 (13.2)	24 (18.0)
>70 to 80	9 (13.8)	13 (19.1)	22 (16.5)
>80 to 90	17 (26.2)	15 (22.1)	32 (24.1)
>90	24 (36.9)	31 (45.6)	55 (41.4)
Baseline BMI [kg/m^2]			
Mean (SD)	31.70 (5.87)	32.27 (5.87)	31.99(5.82)
Baseline BMI, categorical [kg/m^2], N (%)			
<25	8 (12.3)	7 (10.3)	15 (11.3)
25 to <30	19 (29.2)	11 (16.2)	30 (22.6)
≥30	38 (58.5)	50 (73.5)	88 (66.2)
Baseline eGFR (MDRD) [mL/min], N (%)			
≥90	0	0	0
60 to <90	0	0	0
30 to <60	14 (21.5)	5 (7.4)	19 (14.3)
15 to <30	51 (78.5)	63 (92.6)	114 (85.7)
<15	6 (9.2)	8 (11.8)	14 (10.5)

Descriptive statistics of linagliptin pharmacokinetics are reported from a trough plasma sample collected at Visits 2-13 in order to assess linagliptin plasma levels in the patient population included in this trial. The sponsor reported that the median trough concentrations remained fairly stable over time. Categorized by eGFR (MDRD), the mean linagliptin trough levels over time were similar between patients with moderate

renal impairment, severe renal impairment and end stage renal disease, although the number of patients with moderate renal impairment or end stage renal disease was very small. Descriptive statistics of the plasma concentrations are illustrated in the attachment. Mean plasma concentrations are comparable to concentration reported previously in Dr. Jain's review.

The sponsor proposes no labeling additions and changes in the Clinical Pharmacology section.

Reviewer's comment: *This is acceptable from a Clinical Pharmacology perspective. For the safety evaluation in the renal impaired population this reviewer defers to the Clinical division.*

Attachment

Table 15.6.1: 2 Descriptive statistics of linagliptin trough levels (nmol/L) over time by MDRD and eCcr category at baseline - FAS (OR), linagliptin treatment group only

	Linagliptin (N=64)									
	N	Mean	SD	CV	Min	Q1	Median	Q3	Max	gMean	gCV
MDRD - Moderate renal impairment											
Week 4	3	8.97	1.38	15.4	7.83	7.83	8.57	10.50	10.50	8.90	15.11
Week 8	4	14.53	13.12	90.3	6.13	7.44	8.94	21.62	34.10	11.36	87.49
Week 12	3	7.75	0.75	9.7	6.97	6.97	7.82	8.47	8.47	7.73	9.82
Week 18	4	7.81	4.79	61.3	0.76	4.83	9.75	10.80	11.00	5.30	209.77
Week 24	4	8.82	0.38	4.4	8.29	8.57	8.88	9.07	9.21	8.81	4.41
Week 30	4	8.24	1.22	14.8	7.02	7.22	8.18	9.27	9.58	8.17	14.94
Week 36	4	9.11	1.76	19.4	6.75	7.94	9.34	10.28	11.00	8.97	20.78
Week 42	3	8.64	2.05	23.7	6.52	6.52	8.81	10.60	10.60	8.48	24.90
Week 48	3	9.31	2.28	24.5	6.72	6.72	10.20	11.00	11.00	9.10	27.02
MDRD - Severe renal impairment											
Week 4	45	10.08	6.60	65.4	2.61	6.18	7.76	12.00	35.60	8.64	57.36
Week 8	44	9.63	6.42	66.7	2.32	6.40	7.23	10.95	40.80	8.34	54.39
Week 12	45	7.84	3.39	43.3	3.75	5.78	7.06	8.93	24.20	7.33	36.29
Week 18	43	8.37	4.06	48.5	0.61	6.19	7.42	9.92	22.50	7.45	58.40
Week 24	41	8.23	2.86	34.7	2.84	6.46	7.44	9.67	15.90	7.75	36.70
Week 30	41	10.07	6.53	64.8	3.02	6.90	8.46	10.30	34.50	8.80	52.05
Week 36	42	9.14	4.40	48.2	1.24	6.37	8.10	11.30	21.00	8.14	54.85
Week 42	42	9.24	6.16	66.6	1.64	5.92	7.67	10.80	40.80	8.01	56.15
Week 48	40	8.27	4.15	50.1	0.25	5.81	7.60	9.94	21.90	6.78	100.65
MDRD - Endstage renal disease											
Week 4	6	9.39	2.74	29.1	7.18	7.50	8.29	10.80	14.30	9.10	27.00
Week 8	7	9.44	3.06	32.4	6.15	6.96	7.87	11.50	14.60	9.04	32.22
Week 12	6	9.53	1.79	18.8	7.39	8.60	9.21	10.10	12.70	9.40	18.21
Week 18	7	6.63	3.70	55.8	0.93	3.92	6.74	8.42	12.70	5.32	102.71
Week 24	6	9.54	2.23	23.3	7.67	7.97	8.81	10.50	13.50	9.35	22.01
Week 30	6	11.94	7.71	64.5	6.72	7.52	7.76	15.80	26.10	10.39	58.91
Week 36	4	16.33	12.24	75.0	7.11	7.46	12.41	25.20	33.40	13.33	83.39
Week 42	3	10.30	3.16	30.7	7.99	7.99	9.00	13.90	13.90	10.00	29.78
Week 48	4	10.56	7.18	68.0	6.21	6.77	7.36	14.35	21.30	9.20	61.37
eCcr - Mild renal impairment											

MDRD = Estimated glomerular filtration rate, eCcr = Estimated creatinine clearance (Cockcroft-Gault)

Source data: Appendix 16.2, Listing 6.7.1, 8.6, 8.7 zctr\pk_ds.sas 24MAR2011

Table 15.6.1: 2 Descriptive statistics of linagliptin trough levels (nmol/L) over time by MDRD and eCcr category at baseline - FAS (OR), linagliptin treatment group only

	Linagliptin (N=64)									
	N	Mean	SD	CV	Min	Q1	Median	Q3	Max	gMean	gCV
Week 8	2	18.21	22.47	123.4	2.32	2.32	18.21	34.10	34.10	8.89	600.32
Week 12	2	5.84	1.70	29.1	4.64	4.64	5.84	7.04	7.04	5.72	30.13
Week 18	3	9.80	4.03	41.1	6.29	6.29	8.90	14.20	14.20	9.26	42.63
Week 24	3	7.62	2.77	36.4	4.42	4.42	9.21	9.24	9.24	7.22	44.47
Week 30	3	13.50	13.62	100.9	3.99	3.99	7.41	29.10	29.10	9.51	134.59
Week 36	3	9.69	7.02	72.4	4.62	4.62	6.75	17.70	17.70	8.20	78.44
Week 42	2	8.29	5.25	63.3	4.58	4.58	8.29	12.00	12.00	7.41	76.83
Week 48	1	3.98			3.98	3.98	3.98	3.98	3.98	3.98	
eCcr - Moderate renal impairment											
Week 4	25	11.67	7.82	67.0	5.39	7.06	8.12	12.90	35.60	9.97	57.08
Week 8	25	10.27	7.43	72.3	4.33	6.63	7.57	9.94	40.80	8.89	52.06
Week 12	25	8.02	4.00	49.9	4.23	5.78	6.97	8.77	24.20	7.40	39.48
Week 18	25	8.25	4.66	56.5	0.61	6.23	7.71	10.10	22.50	6.69	93.58
Week 24	23	7.80	2.50	32.0	2.84	6.49	7.44	9.63	13.60	7.38	36.36
Week 30	24	10.59	7.02	66.3	4.53	7.03	8.56	10.20	34.50	9.29	49.85
Week 36	24	9.23	5.08	55.0	1.24	6.07	7.91	11.65	21.00	7.90	67.10
Week 42	24	9.18	7.43	80.9	3.80	5.78	6.93	10.45	40.80	7.79	55.51
Week 48	23	8.62	4.88	56.6	0.25	5.83	7.58	12.30	21.90	6.39	146.51
eCcr - Severe renal impairment											
Week 4	26	8.05	3.44	42.8	2.61	5.60	7.26	10.50	16.40	7.38	45.02
Week 8	25	8.94	4.25	47.6	4.65	6.30	6.96	10.20	20.40	8.17	43.49
Week 12	24	7.84	2.14	27.3	3.75	6.26	7.63	9.04	13.70	7.57	28.02
Week 18	23	7.61	3.55	46.7	0.93	5.81	6.93	9.33	19.40	6.79	59.50
Week 24	22	8.84	2.55	28.8	5.51	6.81	8.17	10.50	13.70	8.51	28.66
Week 30	21	8.46	2.97	35.1	3.02	6.72	8.16	8.95	15.80	7.98	37.17
Week 36	20	8.91	2.68	30.1	4.66	7.10	8.56	10.41	17.00	8.57	28.89
Week 42	21	9.49	3.79	39.9	1.64	7.19	8.76	11.40	19.50	8.64	52.61
Week 48	21	8.64	3.87	44.8	5.02	6.07	7.62	9.53	21.30	8.05	36.98
eCcr - Endstage renal disease											
Week 4	3	11.86	2.82	23.8	8.77	8.77	12.50	14.30	14.30	11.62	25.66
Week 8	3	10.36	2.16	20.8	7.87	7.87	11.50	11.70	11.70	10.19	22.70

MDRD = Estimated glomerular filtration rate, eCcr = Estimated creatinine clearance (Cockcroft-Gault)

Source data: Appendix 16.2, Listing 6.7.1, 8.6, 8.7

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Attachment

Table 15.6.1: 2 Descriptive statistics of linagliptin trough levels (nmol/L) over time by MDRD and eCcr category at baseline - FAS (OR), linagliptin treatment group only

	Linagliptin (N=64)									
	N	Mean	SD	CV	Min	Q1	Median	Q3	Max	gMean	gCV
Week 12	3	11.03	2.15	19.5	8.60	8.60	11.80	12.70	12.70	10.88	20.94
Week 18	3	8.99	2.58	28.7	6.74	6.74	8.42	11.80	11.80	8.75	28.77
Week 24	3	11.05	4.31	39.0	7.67	7.67	9.58	15.90	15.90	10.53	38.71
Week 30	3	15.07	9.76	64.8	7.52	7.52	11.60	26.10	26.10	13.16	70.02
Week 36	3	18.87	13.14	69.7	7.81	7.81	15.40	33.40	33.40	15.90	83.47
Week 42	1	8.62			8.62	8.62	8.62	8.62	8.62	8.62	
Week 48	2	8.66	3.46	40.0	6.21	6.21	8.66	11.10	11.10	8.30	42.86

MDRD = Estimated glomerular filtration rate, eCcr = Estimated creatinine clearance (Cockcroft-Gault)

Source data: Appendix 16.2, Listing 6.7.1, 8.6, 8.7

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/s/

IMMO ZADEZENSKY
08/03/2012

JAYABHARATHI VAIDYANATHAN
08/06/2012

Office of Clinical Pharmacology

Memo to File

NDA	201280/S-002
Submission Date	07/22/2011
Brand Name	Tradjenta (Linagliptin)
Memo Date	April 16, 2012
Clinical Pharmacology Reviewer	Manoj Khurana, Ph.D.
Clinical Pharmacology Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolic and Endocrine Products
Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Type; Code	Supplemental NDA; Standard
Formulation; Strength(s)	Oral Tablet, 5 mg Once-daily
Proposed Indication	Treatment of type 2 diabetes mellitus

Boehringer Ingelheim (BI) has submitted an efficacy supplement for Tradjenta (linagliptin) tablets to include information on the 1218.46 trial entitled: "*A Phase III randomized, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naive or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycaemic control*".

This trial was reviewed under linagliptin/metformin fixed dose combination NDA (201281). This submission has no new clinical pharmacology information for review. There are no changes proposed for clinical pharmacology section in the label based on Trial 1218.46. Refer to the clinical review for further details.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANOJ KHURANA
04/17/2012

JAYABHARATHI VAIDYANATHAN
04/17/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 201280/S-002

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: 201280/S-002

Name of Drug: Tradjenta (linagliptin) tablets

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: May 21, 2012 (email)

Receipt Date: May 21, 2012 (email)

Background and Summary Description for 201280/S-002:

Tradjenta is a once-daily, oral, dipeptidyl-peptidase-IV (DPP4) inhibitor approved in May 2011 as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes. Boehringer Ingelheim has submitted the following supplement to the Tradjenta NDA.

- An efficacy supplement (S-002) seeking to update the Tradjenta label with the findings from Trail 1218.46, a 24-week randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of twice daily co-administration of linagliptin 2.5 mg + metformin 500 mg and of twice daily co-administration of linagliptin 2.5 mg + metformin 1000 mg to the individual components of the co-administered drugs (i.e., metformin 500 mg twice daily, metformin 1000 mg twice daily, linagliptin 5 mg once daily) and to placebo.

The efficacy and safety findings for this trial were fully reviewed in NDA 201281 (refer to Dr. Ilan Irony's CDTL memorandum for details). No additional efficacy and safety data for trial 1218.46 were provided with this supplement.

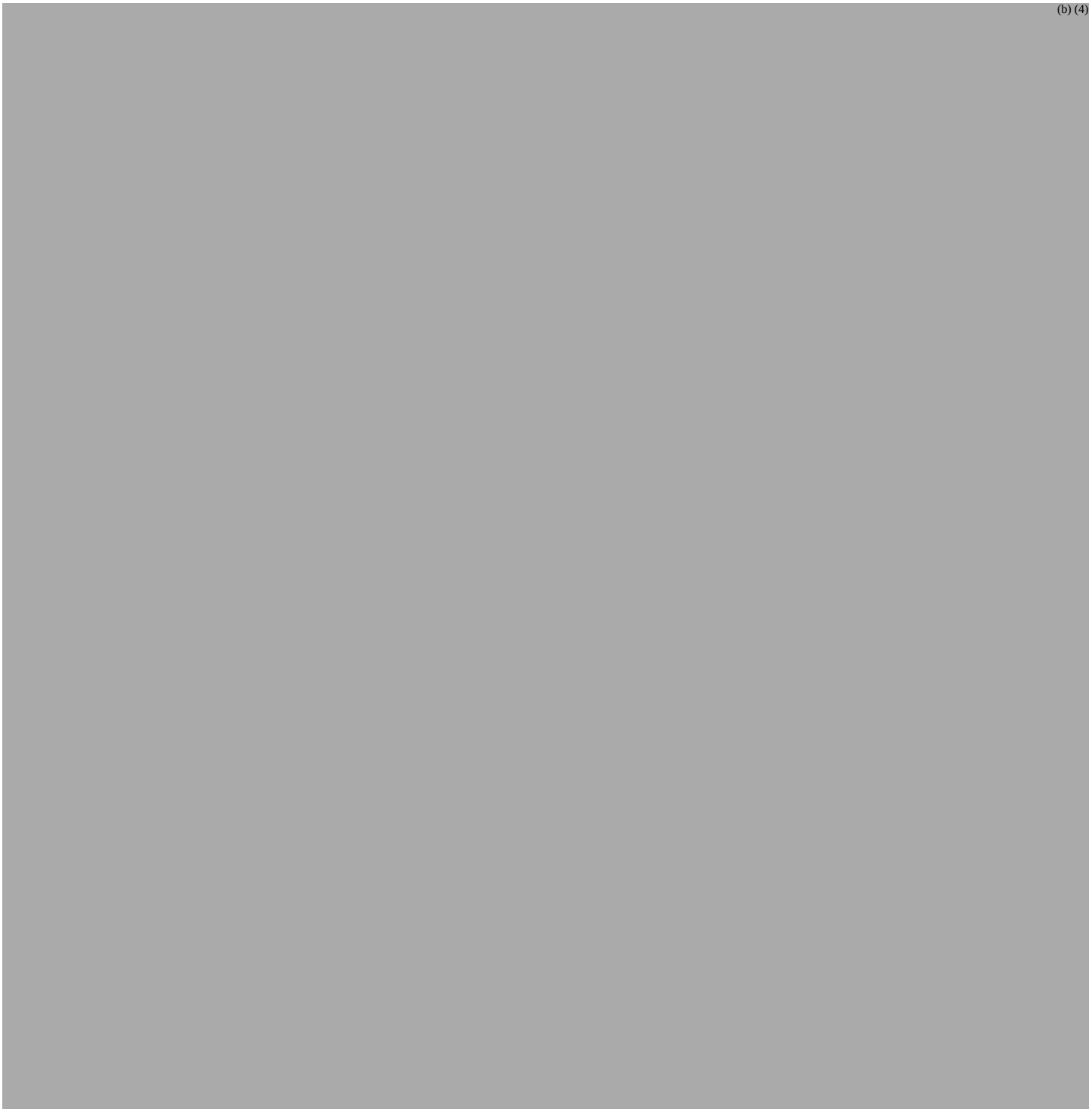
The last approved supplement was S-001, which was approved on November 9, 2011. S-001 provided for revisions to the HOW SUPPLIED/STORAGE AND HANDLING section of the Full Prescribing Information sections of the Tradjenta package insert, with information regarding cartons containing 10 blister cards of 10 tablets each (10 X 10).

The S-001 label for NDA 201280 provides for changes to the **ADVERSE REACTIONS** section of the Highlights of Prescribing Information section and changes to the **ADVERSE REACTIONS, USE IN SPECIFIC POPULATIONS, OVERDOSAGE, CLINICAL PHARMACOLOGY, AND CLINICAL STUDIES** of the Full Prescribing Information

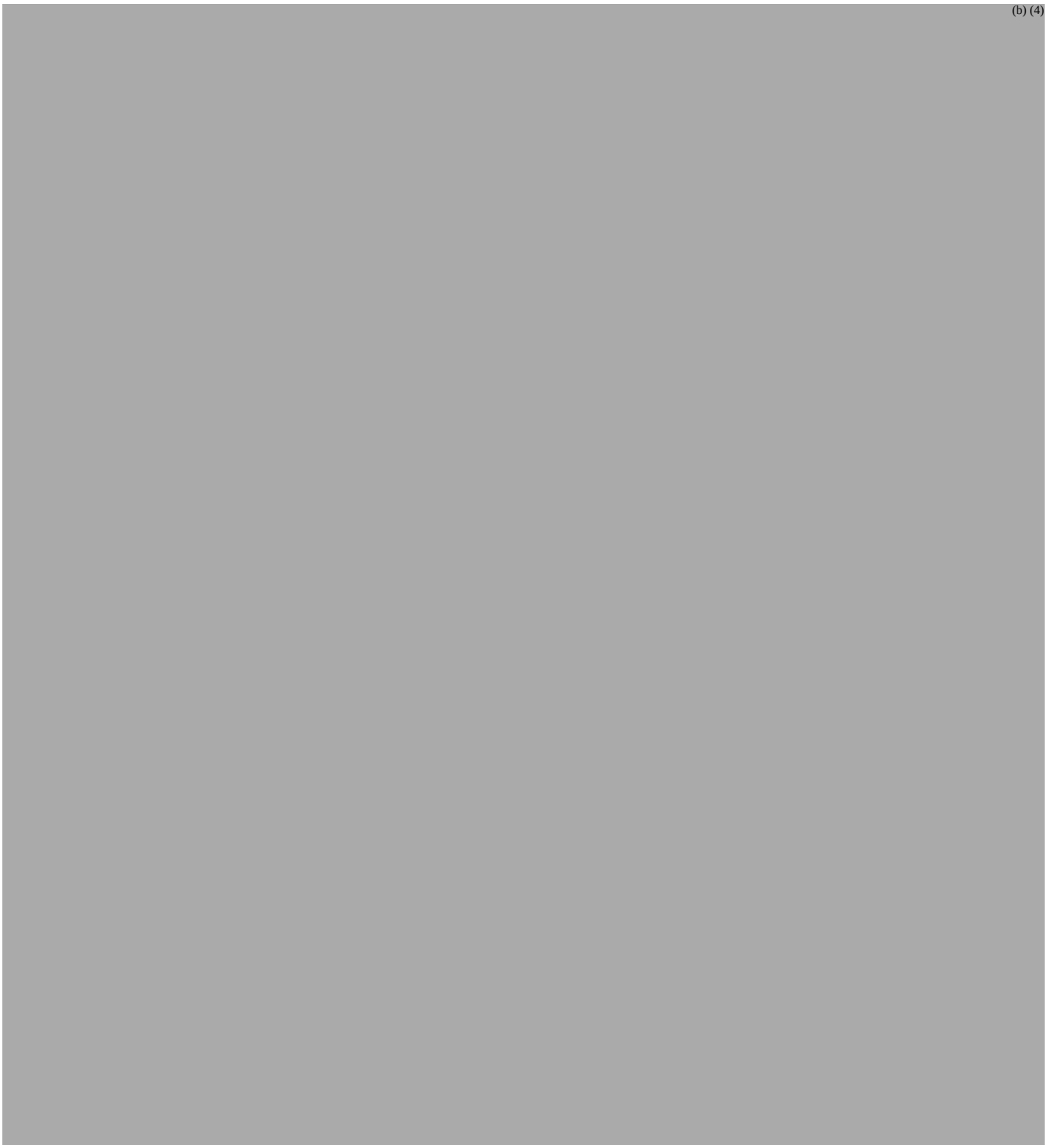
sections of the Tradjenta package insert. In addition, modifications were made to the PPI.

Review of Package Insert/PPI for combined 201280/S-002 labeling
The following revisions were made to the package insert/PPI for NDA 201280/S002. Yellow highlighted information was added. Crossed out information was deleted.

(b) (4)



9 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



Conclusions:

A manual labeling review was completed comparing this label to the last approved labeling for 201280/S001, which was approved on November 09, 2011. The label was consulted to OPDP

(formerly DDMAC) who had no comments regarding the SCPI dated May 3, 2012. The agreed-upon PI/MedGuide emailed by BMS on, May 21, 2012, was accepted by the CDTL, Dr. Jean-Marc Guettier. This agreed-upon PI/MedGuide was forwarded to the Division Director, Dr. Mary Parks for final concurrence. Also attached is SRPI.

Raymond Chiang, MPT, MS, MS

Regulatory Project Manager	Date
Julie Marchick, MPH	
Chief, Project Management Staff	Date

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

INSTRUCTIONS FOR COMPLETING THE SRPI
There is one drop-down menu and one comment field for each item.

Drop-Down Menu: "NO" is the default option. For each SRPI item, click on the word "NO" and choose one of three following options:

- **NO: The PI does not meet the requirement for this item (deficiency).**
- **YES: The PI meets the requirement for this item (no deficiency).**
- **N/A (not applicable): This item does not apply to the specific PI under review.**

Comment Field: Comments are optional. To insert a comment for a particular item, click on the word "*Comment*" and insert your comment.

INSTRUCTIONS FOR COPYING ITEMS FROM SRPI TO 74-DAY OR ADVICE LETTER:

The SRPI is "protected" (or "locked") to allow use of the drop-down menus. However, the "protection" mode does not allow you to directly copy the SRPI item into the 74-day or advice letter.

To copy SRPI items in the letter, after completion of the 48-item SRPI checklist, unprotect (or unlock) the document:

Microsoft Word 2003
(1) Click on the "Tools" tab, then (2) click on "Unprotect Document."

Microsoft Word 2007
(1) Click the "Review" tab, (2) click on "Protect Document", (3) on "Restrict Formatting and Editing" window click "Stop Protection" at the bottom of the window, and (3) click "OK" (leave the password box blank).

If you need to switch from the "unprotected" mode back to the "protected" mode to allow use of the drop-down menus:

Microsoft Word 2003
(1) Click the "Tools" tab (2) click on "Protect Document", (3) click on "Yes, Start Enforcing Protection" in the right-sided task pane, and (4) click "OK" (leave the password box blank).

Microsoft Word 2007
(1) Click the "Review" tab, (2) click on "Protect Document" tab, (3) click on "Restrict Formatting and Editing", (4) click on "Yes, Start Enforcing Protection", and (5) click "OK" (leave the password box blank).

[END INSTRUCTION: DELETE ALL INSTRUCTIONS BEFORE DARRTS CHECK-IN.]

Highlights (HL)

(b) (4)

GENERAL FORMAT

1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

   Comment:

2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

   Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

   - **For the Filing Period (for RPMs)**
     - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
     - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
   - **For the End-of Cycle Period (for SEALD reviewers)**
     - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

   Comment:

3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

   Comment:

4. White space must be present before each major heading in HL.

   Comment:

5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

   Comment:

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information (SRPI)

• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

(b) (4)

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

12. All text must be **bolded**.

Comment:

13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

(b) (4)

14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

24. Each contraindication is bulleted when there is more than one contraindication.
Comment: *Uses same format as FPI*

Adverse Reactions

(b) (4) 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

28. A horizontal line must separate TOC from the FPI.

Comment:

29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

32. All section headings must be **bolded** and in UPPER CASE.

Comment:

(b) (4)

33. All subsection headings must be indented, not bolded, and in title case.

Comment:

34. When a section or subsection is omitted, the numbering does not change.

Comment:

35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

37. All section and subsection headings and numbers must be **bolded**.

Comment:

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

(b) (4)

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

    Comment:

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

    Comment:

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

    Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

42. All text is **bolded**.

    Comment:

43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

    Comment:

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

    Comment:

Contraindications

45. If no Contraindications are known, this section must state "None".

    Comment:

Adverse Reactions

46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"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 clinical practice."

(b) (4)

Comment:

47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *No postmarketing adverse reaction data included*

Patient Counseling Information

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

RAYMOND S CHIANG
05/21/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)

****Pre-decisional Agency Information****

Memorandum

Date: May 7, 2012

To: Raymond Chiang, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer, DPDP
Kendra Y. Jones, Regulatory Review Officer, DCDP

CC: Lisa Hubbard, Group Leader, DPDP
Shefali Doshi, Group Leader, DCDP

Subject: NDA #201280/S-002 Tradjenta™ (linagliptin) Labeling Review

---

OPDP has reviewed the proposed package insert (PI) and patient package insert (PPI) for Tradjenta™(linagliptin) (Tradjenta) originally consulted from DMEP to OPDP on May 1, 2012.

OPDP has reviewed the proposed version of these documents accessed from the eRoom on May 3, 2012 and we do not have any comments at this time.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the PPI, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAMUEL M SKARIAH
05/07/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 201280/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201280 SUPPL # 002 HFD # 510

Trade Name: Tradjenta

Generic Name: linagliptin

Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known: May 22, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 201280 Tradjenta (linagliptin)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Full study report for Trial 1218.46 was submitted. Trial 1218.46 is entitled, “A Phase 3, randomized, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naive or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycemic control.”

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Trial 1218.46 – NDA 201281

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Trial 1218.46 – NDA 201281

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

N/A

==========

Name of person completing form: Raymond Chiang MPT, MS, MS (concurred by Pam Lucarelli 10.16.12)
Title: Regulatory Project Manager
Date: 10.10.12

Name of Office/Division Director signing form: Dr. Jean-Marc Guettier signing on behalf of Dr. Mary Parks
Title: CDTL

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

RAYMOND S CHIANG
11/13/2012

JEAN-MARC P GUETTIER
11/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: **Mail: OPDP (formerly DDMAC)** **Sam Skariah** **Kendra Jones**	FROM: Raymond Chiang Regulatory Project Manager Division of Metabolism and Endocrinology Products X6-1940

DATE May 1, 2012	IND NO.	NDA NO. 201280/S-002	TYPE OF DOCUMENT sNDA efficacy supplement label	DATE OF DOCUMENT 04.30.12

NAME OF DRUG Tradjenta (linagliptin)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Diabetes/lipid-lowering	DESIRED COMPLETION DATE 05.07.12

NAME OF FIRM: BI

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

eRoom Location:
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_2c772

We would like to request OPDP (formerly DDMAC) review the following:

1. PPI and package insert labeling which has already gone through one round of labeling negotiations with the sponsor. Please note that the only substantial change to the PPI was deletion of “or insulin” .

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) DARRTs

Raymond Chiang	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

RAYMOND S CHIANG
05/01/2012

From: Chiang Raymond
To: "heidi.reidies@boehringer-ingelheim.com"
Cc: chung.lee-sogaard@boehringer-ingelheim.com
Subject: RE: Information request for linagliptin efficacy supplement - NDA 201280-Supp 2
Date: Tuesday, April 17, 2012 1:06:17 PM

Hi Heidi,
I left you a voicemail. Is there a cell number I can reach you at?
See below (in black font) additional information request. Please send a response to the request regarding myalgia by this Friday.

Your proposal to keep the label as is regarding the uric acid until you run additional analyses is acceptable. Also these additional analyses (b) (4) can be submitted as an amendment to one of the other pending efficacy supplements (S-003, S-004, S-005).

thanks,

ray

(b) (4) ***In your updated pooled placebo controlled safety database (SAF-2 + 1218.46) an imbalance not favoring linagliptin in myalgia adverse event reporting similar to that seen in the original NDA is still seen (1.7 versus 1.2%). You performed several additional subgroup analyses excluding all trials except monotherapy and add-on to metformin trials. We are aware that the imbalance was seen when linagliptin was co-administered with metformin but it is not clear why you excluded trials 1218.18, and 1218.35 from these subgroup analyses since myalgia is not a reported adverse reaction for sulfonylurea drugs. In your pooled placebo-controlled studies (excluding the renal impairment study) and by treatment arm (linagliptin versus placebo) please provide the following;***

> ***Line listing and narratives, by unique subject ID numbers, of serious adverse events in participants having ever reported myalgia as an adverse event***
>
> ***Line listing and narratives , by unique subject ID numbers, of discontinuations in participants having ever reported myalgia as an adverse event***
>
> ***Line listing by participant ID numbers for other clinically significant events (i.e., rhabomyolysis, myopathy, muscle weakness) not captured by the above two categories***
>
> ***The number of participants having ever reported myalgia who also had elevations in creatinine kinase above the upper limit at anytime in the study***
>
> ***Analyze for the presence baseline risk factors (i.e., medications, medical conditions) for myalgia in the linagliptin versus placebo arm***
>
> ***Describe the time course of myalgia in participants who ever reported myalgia***

In your recent response to our information request you stated that you included data from trial 1218.43 based on snapshot data on April 13, 2010. We do not agree that a study evaluating subjects with severe renal insufficiency should be pooled with SAF-2 + 1218.46 data. Subjects in this study could have elevated uric acid levels due to renal insufficiency and confound the overall results. You had stated that increases in PCSA of uric acid was defined as laboratory value above the upper limit of normal (ULN) during treatment (reference range 2.4 to 6.5 mg/dL). Explain how increases in Potential Clinically Significant Abnormalities (PCSA) of uric acid was determined for subjects in study 1218.43.

In all the studies included in SAF-2 and 1218.46 clarify how the PCSA of uric acid was determined. The reference range of uric acid is higher for man than woman, did you use the same reference range (2.4 to 6.5 mg/dL) for both gender? In your analyses did you consider the baseline uric acid levels, or change from baseline, when determining the PCSA of uric acid? Are subjects who had one uric acid level above the ULN during treatment (regardless of baseline) considered to have had an increase in PCSA of uric acid, even if the level declined to normal level at a subsequent visit during the treatment period?

In subjects ever noted to have increases in PCSA of uric acid [SAF-2 + trial 1218.46; 2.5% (71/2893) in linagliptin versus 1.5% (22/1477) in placebo], provide line listing and narratives for

> ***Serious adverse events and Discontinuations***
>
> ***Provide line listings by unique subject ID numbers for other significant adverse events related to hyperuricemia not captured by serious adverse reactions or discontinuations (i.e., gout, kidney stones etc…)***

In addition compare linaglitpin to placebo for;

> ***The number and proportion of subjects who had persistently elevated uric acid levels***
>
> ***The number and proportion of subjects who required treatment for increased uric acid or clinical sequelae of hyperuricemia (e.g., arthritis)***
>
> ***The presence of baseline imbalance in risk factors for the development of hyperuricemia***

From: heidi.reidies@boehringer-ingelheim.com [mailto:heidi.reidies@boehringer-ingelheim.com]
Sent: Monday, April 16, 2012 4:43 PM
To: Chiang, Raymond
Cc: chung.lee-sogaard@boehringer-ingelheim.com
Subject: FW: Information request for linagliptin efficacy supplement - NDA 201280-Supp 2
Importance: High

Dear Ray,

As we discussed on the telephone earlier today, [redacted] (b) (4) The appropriate individuals to adequately address the Agency's questions below are not readily available to meet the FDA-requested timelines, and we would prefer not to hold up the approval of other proposed labeling changes associated with this sNDA.

Please note that BI intends to gather all relevant information related to [redacted] (b) (4) from the TRADJENTA labeling (including responses to the FDA requests for information below) and submit it as an amendment to one of the other pending efficacy supplements (S-003, S-004, S-005) all of which have action dates in August or in September of this year.

Would the Division have any concerns with this approach?

Kind regards,
Heidi

From: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Sent: Friday, April 13, 2012 1:10 PM
To: Chiang, Raymond
Subject: RE: Information request for linagliptin efficacy supplement - NDA 201280-Supp 2

Dear Ray,

Our response is located after FDA question below. Our server is down and we are not able to provide the supporting documentation today. However, we will provide this next Monday when we respond to the second part of the information request. I hope this is acceptable.

Please let me know if you have any questions.

Best regards,
Chung.

Question 1:

In your submission on September 21, 2011, you stated that the 4-month safety update (4MSU) of the largest available placebo controlled pool (SAF-2) in NDA 201280 included trial 1218.46, and your updated set of placebo controlled studies in this 4MSU (MSU-2) included 2963 subjects being treated

with linagliptin and 1539 patients being treated with placebo. You provided the updated frequency of patients reporting Potential Clinically Significant Abnormalities (PCSA) with uric acid for patients on linagliptin (N=87, 2.9%) and placebo (N=40, 2.6%) based on this 4MSU. The initial PCSA based on SAF-2 was 2.7% (N=68) and 1.3% (N=15) for linagliptin and placebo arms respectively.

However, if you update the SAF-2 of NDA 201280 with the safety data from trial 1218.46 (U10-2372-01, Table 15.3.3.1:4 for PCSA data in uric acid - see below), the frequency of PCSA in uric acid would be 2.5% (N=71 for 2893 subjects) for linagliptin and 1.5% (N=22 for 1477 subjects) for placebo. From trial 1218.46, the updated treatment arms for linagliptin would include Lina5, L2.5+M500, and L2.5+M1000 treatment arms; the updated treatment arms for placebo would include placebo, M500, and M1000 treatment arms.

Explain and clarify this discrepancy.

Table 15.3.3.1: 4 Frequency of patients [N(%)] with possible clinically significant abnormalities - Treated set

SUBSTRATES

Parameter/ Treatment	N	Decrease	Increase
Bilirubin, direct			
Placebo	51	0	0
M500	125	0	0
M1000	101	0	0
Lina5	109	0	0
L2.5+M500	102	0	0
L2.5+M1000	112	0	0
Triglyceride			
Placebo	62	0	4 (6.5)
M500	139	0	4 (2.9)
M1000	136	0	8 (5.9)
Lina5	131	0	4 (3.1)
L2.5+M500	133	0	8 (6.0)
L2.5+M1000	140	0	8 (5.7)
Uric acid			
Placebo	62	0	2 (3.2)
M500	139	0	1 (0.7)
M1000	136	0	4 (2.9)
Lina5	131	0	1 (0.8)
L2.5+M500	133	0	1 (0.8)
L2.5+M1000	140	0	1 (0.7)
Protein, total			
Placebo	62	0	0
M500	139	0	0
M1000	136	0	0
Lina5	131	0	0
L2.5+M500	133	0	1 (0.8)
L2.5+M1000	140	0	0

BI response:
The discrepancy is due to the additional subjects with PCSA of uric acid from the 1218.43 study based on data from a snapshot taken on April 13, 2010.

Our response regarding PCSA of uric acid submitted on September 11, 2011 included an additional 16 subjects to the linagliptin arm/18 subjects to the placebo arm from the 1218.43 study, and an additional 3 subjects to the linagliptin arm/7 subjects to the placebo arm from the 1218.46 study (SEQ 55). Additional documentation to support this will be provided together with our response to the second part of FDA's information request (Provide the frequency of PCSA of uric acid reported in the pooled SAF-2 dataset by each individual study) on Monday, April 16th.

Table 1

Source	Linagliptin	Placebo
Initial PCSA based on SAF-2 (SEQ 0000)	68	15
1218.46 final CTR, Table 15.3.3.1:4 (SEQ 45, sNDA)	3	7
1218.43 snapshot	16	18
Total (4SMU)	87 (2.9%)	40 (2.6%)

Chung Lee-Søgaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262
Email: chung.lee-sogaard@boehringer-ingelheim.com

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Tuesday, April 10, 2012 10:54 AM
To: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Subject: FW: Information request for linagliptin efficacy supplement - NDA 201280-Supp 2

Hi Chung,
See information request below (in black font) from the FDA clinical reviewer. Because of the pending PDUFA date, she requests a response within 3 days.

In your submission on September 21, 2011, you stated that the 4-month safety update (4MSU) of the largest available placebo controlled pool (SAF-2) in NDA 201280 included trial 1218.46, and your updated set of placebo controlled studies in this 4MSU (MSU-2) included 2963 subjects being treated with linagliptin and 1539 patients being treated with placebo. You provided the updated frequency of patients reporting Potential Clinically Significant Abnormalities (PCSA) with uric acid for patients on linagliptin (N=87, 2.9%) and placebo (N=40, 2.6%) based on this 4MSU. The initial PCSA based on SAF-2 was 2.7% (N=68) and 1.3% (N=15) for linagliptin and placebo arms respectively.

However, if you update the SAF-2 of NDA 201280 with the safety data from trial 1218.46 (U10-2372-01, Table 15.3.3.1:4 for PCSA data in uric acid - see below), the frequency of PCSA in uric acid would be 2.5% (N=71 for 2893 subjects) for linagliptin and 1.5% (N=22 for 1477 subjects) for placebo. From trial 1218.46, the updated treatment arms for linagliptin would include Lina5, L2.5+M500, and L2.5+M1000 treatment arms; the updated treatment arms for placebo would include placebo, M500, and M1000 treatment arms.

Explain and clarify this discrepancy.

Table 15.3.3.1: 4 Frequency of patients [N(%)] with possible clinically significant abnormalities - Treated set

SUBSTRATES

Parameter/ Treatment	N	Decrease	Increase
Bilirubin, direct			
Placebo	51	0	0
M500	125	0	0
M1000	101	0	0
Lina5	109	0	0
L2.5+M500	102	0	0
L2.5+M1000	112	0	0
Triglyceride			
Placebo	62	0	4 (6.5)
M500	139	0	4 (2.9)
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L2.5+M1000	140	0	1 (0.7)
Protein, total			
Placebo	62	0	0
M500	139	0	0
M1000	136	0	0
Lina5	131	0	0
L2.5+M500	133	0	1 (0.8)
L2.5+M1000	140	0	0

Provide the frequency of PCSA of uric acid reported in the pooled SAF-2 dataset by each individual study in the table provided below.

Table: Frequency of patients with PCSA of uric acid in each study included in SAF-2

Study	Linagliptin			Placebo		
	Subjects with PCSA of increase in uric acid	N	%	Subjects with PCSA of increase in uric acid	N	%
1218.2						
1218.3						
1218.5						
1218.6						
1218.15						
1218.16						
1218.17						
1218.18						
1218.23						
1218.35						
1218.37						
1218.50						
Total	*68*	*2489*	*2.7*	*15*	*1140*	*1.3*

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/s/

RAYMOND S CHIANG
04/17/2012

From: Marchick, Julie
To: Suggs, Courtney;
cc: Galliers, Enid M; Chiang, Raymond;
Subject: RE: Submissions that may require PeRC review
Date: Friday, November 04, 2011 11:28:22 AM

Hi Courtney,

These supplements do not trigger PREA and are not in response to a PREA PMR.

Thanks,
Julie

From: Suggs, Courtney
Sent: Friday, November 04, 2011 10:40 AM
To: Galliers, Enid M; Marchick, Julie
Subject: Submissions that may require PeRC review

Dear Enid and Julie,

The following submissions have a PDUFA goal date in the near future. Please help us by letting us know if these applications trigger PREA or are in response to a PREA post-marketing commitment/requirement.

201280 LABEL W CLIN 2 Tradjenta (linagliptin) Tablets DMEP OS
7/22/2011 S 5/22/2012
201280 LABEL W CLIN 3 Tradjenta (linagliptin) Tablets DMEP OS
10/14/2011 S 8/14/2012

As a reminder, PREA triggers include the following

New active ingredient
New dosage form
New route of administration
New indication
New dosing regimen

If PREA is triggered for any of these submissions or if they are in response to a

PREA postmarketing commitment/requirement, contact Courtney Suggs or George Greeley to schedule a time for PeRC to review. Please let me know if your division plans to act early on this application so we can plan a PeRC date prior to approval.

Thanks,
Courtney

Courtney M. Suggs, Pharm.D., MPH

LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
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Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

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/s/

RAYMOND S CHIANG
11/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201280/S-002

FILING COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Maureen Oakes, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Oakes:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 22, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tradjenta (linagliptin) tablets, 5mg.

This supplemental application proposes to include information on the 1218.46 trial entitled: "A Phase III randomised, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naive or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycaemic control."

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is May 22, 2012.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 22, 2012.

During our filing review of your supplemental application, we identified the following potential review issue:

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RAYMOND S CHIANG
09/12/2011
Signing on behalf of Dr. Mary Parks

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201280/S-002

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Maureen Oakes, Pharm.D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Oakes:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA NUMBER: 201280

SUPPLEMENT NUMBER: 002

PRODUCT NAME: Tradjenta (linagliptin) tablets, 5mg

DATE OF SUBMISSION: July 22, 2011

DATE OF RECEIPT: July 22, 2011

This supplemental application proposes the following change(s): to include information on the 1218.46 trial entitled: "A Phase III randomised, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naive or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycaemic control."

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 20, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please call me at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RAYMOND S CHIANG
09/11/2011