CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201280Orig1s000

CHEMISTRY REVIEW(S)

NDA 201280

CMC Director Review

Tradjenta*

(Linagliptin) Tablets

*This proposed name has not yet been finalized in negotiations between the Agency and Boehringer Ingelheim.

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Boehringer Ingelheim Pharmaceuticals, Inc.

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Presentation: The proposed market packages for the 5 mg tablets are 60 cc HDPE bottles containing 30 or 90 tablets and 375 cc HDPE bottles containing 1,000 tablets (intended for dispensing at mail order pharmacies). All of the bottles are equipped with a child resistant, senior friendly closure with an induction foil seal liner, and a silica gel desiccant packet.

Establishments Evaluation Report (EER) Status: Acceptable

Consults:

EA –	Acceptable
Statistics –	N/A
Methods Validation –	Acceptable
Biopharm–	Acceptable

Microbiology –	N/A
Pharm Toxicology –	Acceptable

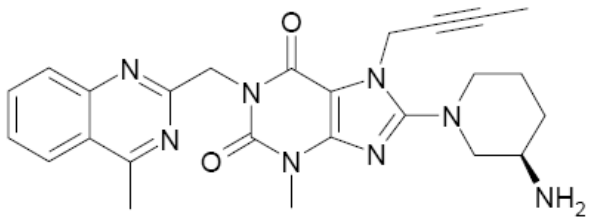
Original Submission:	July 02, 2010
Re-submissions:	N/A
Post-Approval CMC Agreements:	None at this time.

Drug Substance

The drug substance, linagliptin, is a new molecular entity manufactured through a series of chemical synthetic steps, by Boehringer Ingelheim Pharma GmbH & Co. KG in Germany, and the relevant CMC issues related to the manufacture of this material are described in the Drug Substance section of the Chemistry Assessment. Linagliptin is a crystalline white to yellowish solid, which has been found to exist (b) (4) . Boehringer Ingelheim classifies this drug substance as a Class III compound according to the Biopharmaceutical Classification System (BCS) because of its high solubility and low bioavailability. Linagliptin shows high solubility (> 1 mg/ml) in aqueous media up to pH 8. Adequate drug substance specifications were provided which included acceptance criteria for Appearance, Identification, Melting Temperature, Organic Impurities, Organic Volatile Impurities, Enantiomeric Purity, Residual Solvents, Water Content, (b) (4) Assay, and Particle Size Distribution.

The NDA contains satisfactory stability data to support a retest date of (b) (4) for the drug substance for storage at 25°C/60 % R.H.

Molecular Structure:



Chemical Abstracts Name:	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]-
Molecular Formula:	$C_{25}H_{28}N_8O_2$
Molecular Mass:	472.54 g/mol

Drug substance is satisfactory

Drug product

The drug product, with the proposed the proprietary name TRADJENTA and the established name Linagliptin, is a dipeptidyl peptidase-4 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

The manufacturing process of linagliptin film-coated tablets is a standard process

(b) (4)

The dosage form is a 5.0 mg immediate release film-coated tablet that is light red, round, biconvex, bevel-edged with one side debossed with the Boehringer Ingelheim company symbol and the other side debossed with 'D5'.

(b) (4)

An adequate drug product specification was provided which included acceptance criteria for the Description of the dosage form, Identification of the active ingredient, Loss on Drying, Dissolution, Uniformity of Dosage Units, Assay, and Degradation Products. The proposed market packages for the 5 mg tablets are 60 cc HDPE bottles containing 30 or 90 tablets and 375 cc HDPE bottles containing 1,000 tablets.

Besides linagliptin, the drug product contains 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. All of the inactive ingredients are compendial.

Drug product is satisfactory

Overall Conclusion: From CMC point of view, the NDA is recommended for approval.

Eric P Duffy, Ph.D.
Director, Division III
ONDQA/CDER/FDA

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/s/

ERIC P DUFFY
03/14/2011

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