

**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

<b>Consults:</b>	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.

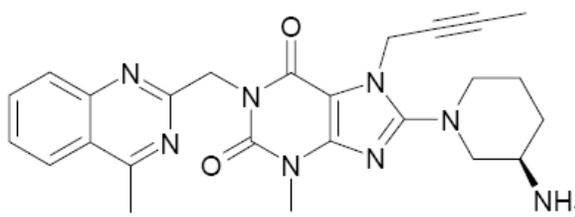
### Drug Substance

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)

(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-piperidiny]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazoliny)methyl]-

Molecular Formula: C<sub>25</sub>H<sub>28</sub>N<sub>8</sub>O<sub>2</sub>

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.

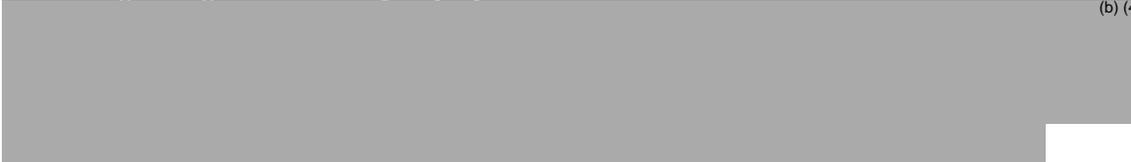
The manufacturing process of linagliptin film-coated tablets is a standard process

(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

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

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/s/  
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ERIC P DUFFY  
03/14/2011

**NDA 201-280**

**Tradjenta\***  
**(Linagliptin) Tablets**

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

**Boehringer Ingelheim Pharmaceuticals, Inc**

**Sheldon Markofsky, Ph.D.**

**and**

**Olen Stephens, Ph.D.**

[For sections P.2, P.3, and P.4]

**Division of Metabolism and Endocrine Products (HFD-510)**

**and**

**Office of New Drug Quality Assessment III**  
**Branch VII**

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Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 201-280
2. REVIEW #: 2
3. REVIEW DATE: 07-March- 2011
4. REVIEWER: Sheldon Markofsky, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	02-July-2010
Filing Review Document	08-Aug-2010
Amendment	23-Sept.-2010
IR Letter	08-Dec-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Original	02-July-2010
Amendment <sup>a</sup>	06-Jan-2011
Amendment <sup>b</sup>	27-Jan-2011
Amendment <sup>c</sup>	01-Feb-2011

- a) The 1-6-11 amendment provides a number of responses to our IR Letter of 12-8-2010.
- b) The 1-27-11 amendment provides the additional responses to our IR Letter of 12-8-2010.
- c) The 2-1-11 amendment provides up-dated container related labels.

7. NAME & ADDRESS OF APPLICANT:

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

Representative: Maureen Oakes, Associate Director, DRA  
Telephone: 203-798-5723

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TRADJENTA (This proposed name has not yet been finalized in negotiations between the Agency and Boehringer Ingelheim.)  
b) Non-Proprietary Name: Linagliptin tablets  
c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Treatment of type 2 diabetes mellitus

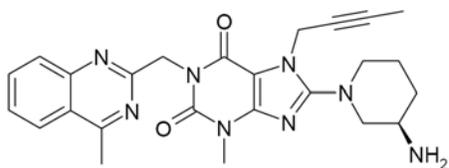
11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OT15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{25}H_{28}N_8O_2$   
472.54 g/mol.

**INN:** Linagliptin**USAN:** Linagliptin

Chemical names:

(Chemical Abstracts)

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]-

(IUPAC) and (INN)

8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-yn-1-yl-3-methyl-1- [(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine- 2,6-dione

CAS Registry Number 668270-12-0

Company Code Number BI 1356 BS

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	9-15-00 and 9-23-05	Reviewed by Don Klein
	III			3	Adequate	3-24-10	Reviewed by R. Agarwal
	III			4	Adequate		See Chemistry Review #1 of this NDA.
	III			3	Adequate	9-27-00	Reviewed by R. Lostritto

**Chemistry Review Data Sheet**

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,963	IND for Linagliptin

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	8-9-10	
Pharm/Tox	Acceptable	3-6-11	David Carlson
Methods Validation	Acceptable	12-30-10	S. B. Markofsky
EA	Acceptable	12-30-10	S. B. Markofsky
Microbiology	N/A		
ONDQA Dissolution Review	Acceptable	2-28-11	Sandra Suarez)-Sharp

19. ORDER OF REVIEW: N/A (OGD Only)

## The Executive Summary

# The Chemistry Review for NDA 201-280

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved,

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product and Drug Substances

#### 1) 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 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)

(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 (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 silica gel desiccant packets. Physician samples are aluminum/aluminum push-through blisters containing 7 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.

## 2) Drug Substance

The drug substance, linagliptin, is manufactured 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)

(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. In this connection, linagliptin shows high solubility (> 1 mg/ml) in aqueous media up to pH 8. An adequate drug substance specification was 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. Satisfactory stability data was provided to support a retest date of (b) (4) for the drug substance for storage at 25°C/60 % R.H.

From a Chemistry, Manufacturing, and Controls (CMC) point of view, the drug substance can be deemed acceptable.

### B. Description of How the Drug Product is Intended to be Used

The recommended (and maximum) dose of TRADJENTA, for the Treatment of type 2 diabetes mellitus, is one 5 mg tablet once daily, without regard to foods. The stability studies support an expiration-dating period of 30 months for TRADJENTA 5 mg tablets when stored at controlled room temperature [25°C (77°F)], with excursions permitted between 15°C and 30°C packaged in all of the proposed commercial container closure systems. Consequently, a 30 month expiry is granted.

## C. Basis for Approvability or Not-Approval Recommendation

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved on the following basis:

- Adequate information was provided in the NDA for the synthesis, purification and controls of the drug substance
- Adequate manufacturing information to support the proposed to-be-marketed drug product
- Adequate specifications and controls for the drug product
- Satisfactory methods to support lot release and stability monitoring of the drug product
- Adequate stability package to support the recommended expiry period of the drug product
- An acceptable Establishment Inspection Report for the relevant facilities employed for the manufacture and testing of the drug substance and the drug product

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

### III. Administrative

#### A. Reviewer's Signatures

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)  
Olen Stephens, Ph.D. (Chemistry Reviewer)

#### B. Endorsement Block (OGD only)

N/A

#### C. CC Block (OGD only)

N/A

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/s/  
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SHELDON B MARKOFSKY  
03/07/2011

ALI H AL HAKIM  
03/07/2011

# **NDA 201-280**

## **Tarjenta\*** **(Linagliptin) Tablets**

\* Boehringer Ingelheim has not yet finalized (selected) this proposed name.

**Boehringer Ingelheim Pharmaceuticals, Inc**

**Sheldon Markofsky, Ph.D.**  
**and**

**Olen Stephens, Ph.D.**

[For sections P.2, P.3, and P.4 related to Quality by Design (QBD)]

**Division of Metabolism and Endocrine Products (HFD-510)**

**and**

**Office of New Drug Quality Assessment III**  
**Branch VII**

File: 201280Rev2

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R REGIONAL INFORMATION.....	N/A
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Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 201-280
2. REVIEW #: 1
3. REVIEW DATE: 30-December- 2010
4. REVIEWER: Sheldon Markofsky, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA (Original)	02-July-2010
Filing Review Document	08-Aug-2010
Amendment	23-Sept.-2010
IR Letter	07-Dec-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA Original	02-July-2010
Amendment <sup>a</sup>	23-Sept.-2010
Amendment <sup>b</sup>	06-Jan-2011

- a) The 9-23-10 amendment provides up-dated packaging information.  
b) The 1-6-11 amendment provides a number of responses to our IR Letter of 12-7-2010.

7. NAME & ADDRESS OF APPLICANT:

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

Representative: Maureen Oakes, Associate Director, DRA

Telephone: 203-798-5723

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TARJENTA (The applicant has not yet finalized (selected) this proposed name.)  
b) Non-Proprietary Name: Linagliptin tablets  
c) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type:1

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of type 2 diabetes mellitus

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5 mg

13. ROUTE OF ADMINISTRATION: Oral

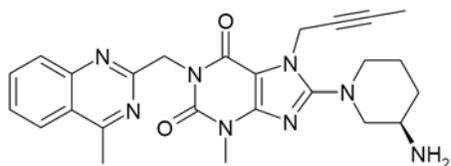
14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{25}H_{28}N_8O_2$   
472.54 g/mol.

**INN:** Linagliptin

**USAN:** Linagliptin

Chemical names:

(Chemical Abstracts)

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]-

(IUPAC) and (INN)

8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-yn-1-yl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine- 2,6-dione

CAS Registry Number 668270-12-0

Company Code Number BI 1356 BS

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	9-15-00 and 9-23-05	Reviewed by Don Klein
	III			3	Adequate	3-24-10	Reviewed by R. Agarwal
	III			4	Adequate		
	III			3	Adequate	9-27-00	Reviewed by R. Lostritto

### Chemistry Review Data Sheet

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

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6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,963	IND for Linagliptin

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	8-9-10	
Pharm/Tox	Pending		David Carlson
Methods Validation	Acceptable	12-30-10	S. B. Markofsky
EA	Acceptable	12-30-10	S. B. Markofsky
Microbiology	N/A		
ONDQA Dissolution Review	Acceptable	Not yet finalized	Sandra Suarez)-Sharp

19. ORDER OF REVIEW: N/A (OGD Only)

## The Executive Summary

# The Chemistry Review for NDA 201-280

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved, pending acceptable responses to our information Request, dated 12-8-2010.

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product and Drug Substances

#### 1) Drug Product

The drug product, with the proposed the proprietary name TARJENTA 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 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)

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## 2) Drug Substance

The drug substance, linagliptin, is manufactured 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)

(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. In this connection, linagliptin shows high solubility (> 1 mg/ml) in aqueous media up to pH 8. Satisfactory stability data was provided to support a retest date of (b) (4) for the drug substance for storage at 25°C/60 % R.H.

From a Chemistry, Manufacturing, and Controls (CMC) point of view, the drug substance can be deemed acceptable pending adequate responses to our information Request, dated 12-8-2010. We anticipate that the outstanding CMC issues can be readily resolved.

### B. Description of How the Drug Product is Intended to be Used

The recommended (and maximum) dose of TARJENTA, for the Treatment of type 2 diabetes mellitus, is one 5 mg tablet once daily, without regard to foods. The stability studies support an expiration-dating period of 30 months for TARJENTA 5 mg tablets when stored at controlled room temperature [25°C (77°F)], with excursions permitted between 15°C and 30°C packaged in all of the proposed commercial container closure systems. Consequently, a 30 month expiry is granted.

### C. Basis for Approvability or Not-Approval Recommendation

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA is approvable at this time pending adequate responses to our Information Request

Letter. We anticipate that the outstanding CMC issues can be readily resolved.

### **III. Administrative**

#### **A. Reviewer's Signatures**

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)  
Olen Stephens, Ph.D. (Chemistry Reviewer)

#### **B. Endorsement Block (OGD only)**

N/A

#### **C. CC Block (OGD only)**

N/A

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SHELDON B MARKOFSKY  
02/02/2011

ALI H AL HAKIM  
02/02/2011

Initial Quality/CMC Assessment  
ONDQA

**Division of Metabolism and Endocrinology Products**

**NDA:** 201280

**Applicant:** Boehringer Ingelheim Pharmaceuticals Inc.

**Stamp Date:** 02-JUL-2010

**PDUFA Date:** 02-MAY-2011

**Proposed Proprietary Name:** Ondero

**Established Name:** linagliptin

**Dosage form and strength:** Immediate release tablet –  
5 mg

**Route of Administration:** oral

**Indications:** Treatment of type 2 diabetes

**CMC Lead:** Su (Suong) Tran, ONDQA

**ONDQA Fileability:** Yes

Initial Quality/CMC Assessment  
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
CBER	<i>Not applicable</i>
CDRH	<i>Not applicable</i>
Compliance (DMPQ)	EER was sent to Compliance by ONDQA PM on 11-JUL-2010.
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>Not applicable</i>
OBP	<i>Not applicable</i>
ONDQA Biopharm	Review of all dissolution/drug release-related information. <i>Assignment: S. Suarez Sharp as of 07-JUL-2010.</i>
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Pharm/Tox	Review of qualification information in support of limits on impurities in the drug substance.
QbD	The application includes information on DoEs in support of the manufacturing design space (the ONDQA IO was notified on 07-JUL-2010).

This is a 505(b)(1) application. The associated IND is IND 70963.

The drug substance linagliptin is a New Molecular Entity (NME) and a small synthetic compound. It is xanthine-derived and an inhibitor of the dipeptidyl peptidase-4 enzyme. The structure has the R configuration at the chiral carbon of the 3-aminopiperidine group.

The drug product is a 5 mg immediate-release tablet. The inactive ingredients are: 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. The commercial packaging consists of bottles of 30-count, 90-count, and 1000-count. A physician sample will be available as a 7-count blister card. The product is stored at room temperature.

**Maximum daily dose is 5 mg linagliptin.**

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### **Has all information requested during the IND phases, and at the pre-NDA meetings been included?**

The NDA includes some information as requested by FDA during the IND development. There is no item-by-item response to FDA's comments, which makes it difficult to assess in the limited time allotted for this filing memo/IQA whether the applicant has provided a satisfactory response to each question. The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed. The reviewer will also confirm that information previously agreed upon by FDA and the sponsor has not been changed in its final version in the NDA (for example, specifications, packaging systems, etc.)

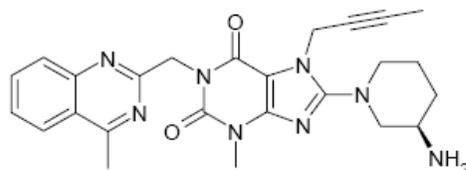
Major issues discussed in the FDA letter dated 29-MAY-2008 include:

- FDA agreed that the starting materials of the drug substance synthesis are compounds (b) (4)  
[REDACTED]
- The NDA will include the study report on polymorphs as well as results of (b) (4)  
[REDACTED] present in the nonclinical and clinical batches. The information will support the sponsor's request not to test for polymorphs in the drug substance specification.
- The NDA will include safety information on impurity limits that exceed the applicable ICH thresholds and data to support the sponsor's claim that particle size has no impact of critical quality attributes and bioavailability.
- The NDA will include a justification for the lack of chiral testing of the drug product.

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**Drug substance:**

Structural Formula:



Chirality: Linagliptin has one chiral center. The corresponding S-enantiomer is named BI 1355 BS.

Molecular Formula:  $C_{25}H_{28}N_8O_2$

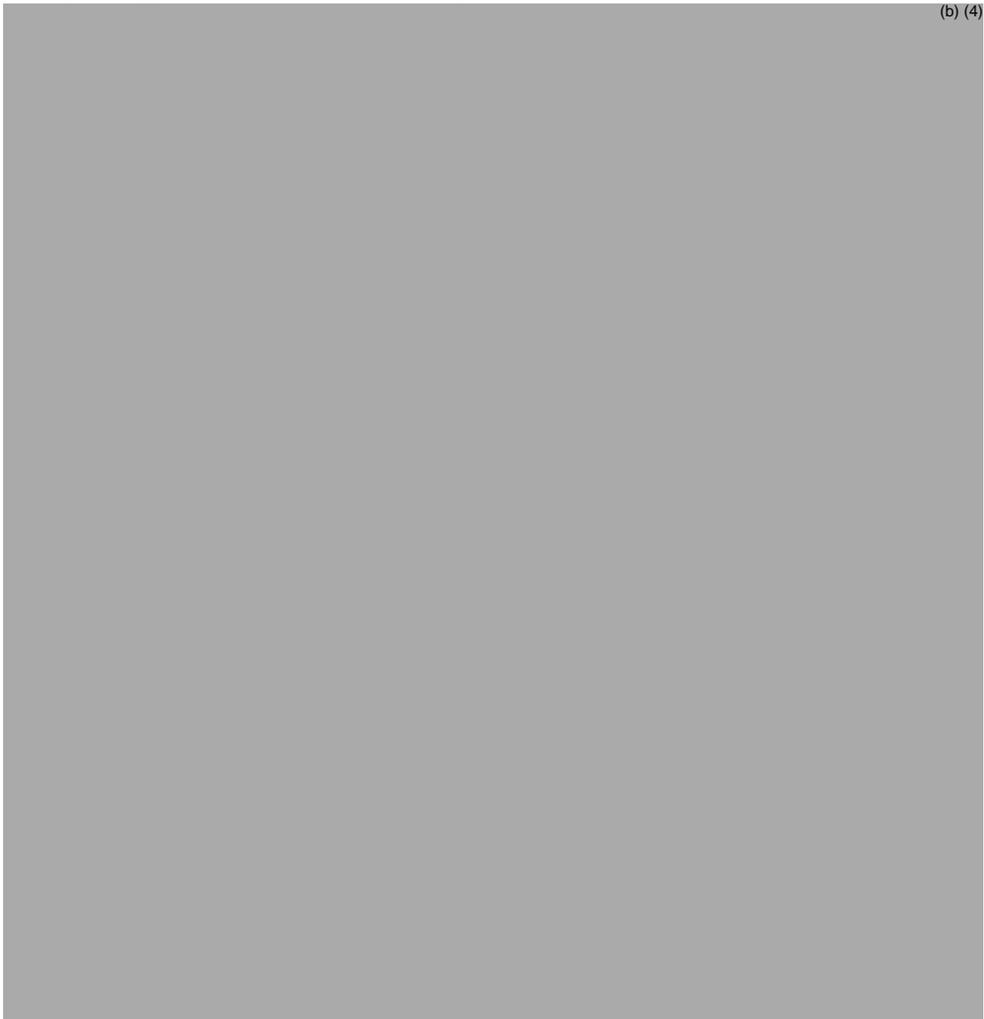
Molecular Mass: 472.54 g/mol

International Non-proprietary Name (INN)	Linagliptin
US Adopted Name (USAN)	Linagliptin
Japanese Accepted Name (JAN)	not yet assigned
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]-
Chemical Name (IUPAC)	8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-yn-1-yl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione
Chemical Name (INN)	8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione
CAS Registry Number	668270-12-0
Company Code Number	BI 1356 BS

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Physical Appearance: white to yellowish solid substance

(b) (4)



**Review comments:** (The drug substance synthesis and specification are copied on pages 17-18)

- **Manufacturing process.** The applicant states that the commercial process is “Variant II/E”, which was used to produce the drug substance for all of the Phase 3 clinical batches.
- **Polymorphism.** Under the conditions of the commercial manufacturing process,  (b) (4) . The applicant claims that polymorphism should have no impact on the in vivo performance of the product because it has no effect on solubility, dissolution, stability, or melting temperature. As previously requested by FDA, the NDA includes the study report on polymorphs as well as results of the forms and mixtures present in the nonclinical and clinical batches. The applicant does not include testing for polymorphs in the drug substance specification. The primary

## Initial Quality/CMC Assessment ONDQA

reviewer will evaluate the information and determine if the omission of polymorph testing is adequately justified.

- **Chirality.** Linagliptin has the R configuration at the chiral carbon of the 3-aminopiperidine group. The drug substance specification includes identity testing by chiral HPLC and a limit of (b) (4) for the S-enantiomer.
- **Particle size.** The drug substance specification includes the acceptance criteria of (b) (4) less than/equal to (b) (4). The reviewer will evaluate the data in the drug product section of the NDA to verify the applicant's claim that particle size has no impact of critical quality attributes and bioavailability.
- **Impurities.** The structures of major impurities are copied on page 19 of this review. Most impurities have limits above the ICH qualification threshold of 0.15% (see below), and the applicant states that these levels are qualified as reported in the toxicology section 2.6.6 (issue to be conveyed to the PharmTox team at the filing meeting). Only (b) (4) is a degradant. All impurities were evaluated for genotoxicity potential (the applicant refers to the toxicology section 2.6.6). Only (b) (4) is identified as potentially genotoxic. The applicant states that batch data and spiking experiments show that the commercial manufacturing process yields (b) (4) levels of less than (b) (4), which is less than the TTC of 1.5 mcg per day (maximum daily dose of 5 mg linagliptin).



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**Drug product**

The composition of the drug product is copied below.

Table 13                      Qualitative and quantitative composition of linagliptin film-coated tablets, 5 mg

Part of tablet	Ingredient	[mg/coated tablet]	Function	Reference to Standards
Tablet core	Linagliptin	5.000	Active	Company Standard
	Mannitol	(b) (4)		USP
	Pregelatinized Starch			NF
	Corn Starch			NF
	Copovidone			NF
	Magnesium stearate			NF
	(b) (4)			USP
Coating			Company Standard	
				USP
	<b>Total weight</b>	<b>185.000</b>		

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



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**Review comments:**

- **BCS class.** The applicant proposes linagliptin to be BCS Class 3. The designation will be evaluated jointly by the ClinPharm team (permeability data in section 4.2.2.2) and CMC team (solubility data in section 2.3.S.3.1).
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** Phase 3 clinical studies were conducted with the “intended final formulation” or iFF. The commercial formulation is different from iFF [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] The applicant considers the change to be a level 1 change per SUPAC-IR. The 3 primary stability batches have the commercial formulation. Supportive stability batches are Phase 3 iFF clinical batches.

**Manufacturing process of the drug product**



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**Review comments:**

**Quality by Design.** The application has information on DoEs that were conducted to establish the design space copied below: (the ONDQA IO was notified on 07-JUL-2010)

(b) (4)

**Master batch records.** The commercial master batch records are included in the NDA.

**Comparability of the product used in the clinical studies, stability studies, and commercial product.** All Phase 3 clinical and supportive stability batches were manufactured at the process development site Boehringer Ingelheim Biberach, Germany (BIBIC). The primary stability batches were manufactured at production scale at the commercial site Boehringer Ingelheim Roxane Inc., US (BIRI). The applicant states that only minor process adaptations were made during the process transfer to accommodate available equipment sizes. The 2 manufacturing sites are bridged via comparative dissolution and batch release data (to be assessed by the primary reviewer). The dissolution data were obtained using only 0.1 M HCl as medium; the adequacy of the data will be evaluated by the ONDQA Biopharm team.

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**Drug product specification**

The proposed drug product specification is copied on page 22 of this review.

**Review comments:**

- **Limits on degradation products.** The proposed limit on the degradant (b) (4) which is below the ICH qualification threshold of 1.0% for the maximum daily dose of 5 mg linagliptin. A limit of (b) (4) is proposed for an unknown degradant, which is below the ICH identification threshold of 0.5% for this product.
- **Chirality.** No chiral testing is included in the drug product specification. The applicant states that ICH Q6A was followed in determining that such testing is unnecessary. The reviewer will evaluate all available data to confirm that linagliptin does not racemize during the product manufacture and on stability.
- **Dissolution.** The ONDQA Biopharm will review all dissolution/drug release-related information.  
*Assignment: S. Suarez Sharp as of 07-JUL-2010.*
- **Tablet hardness.** This test is conducted as an in-process control.
- **Microbial limits.** No microbial testing is included in the drug product specification. The applicant states that microbial and water activity data per ICH Q6A support the omission of this testing, which will be confirmed by the reviewer.

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**Container closure systems for product distribution**

The container closure system is comprised of a 60 cc or 375 cc high density polyethylene (HDPE) bottle (b) (4), a closure with an induction foil seal liner and silica gel packets (b) (4). The closure of the smaller bottle is child resistant and senior friendly (b) (4) as this packaging configuration is dispensed directly to the patient. The closure of the 375 cc bottle is covered by DMF (b) (4). Only the foil seal liner of the closure comes in direct contact with the tablets.

Physician samples are packaged in blister cards with individually molded cavities. These cards consist of an aluminium lidding foil (b) (4) and an aluminium based bottom foil (b) (4). The surface of the blister in contact with the product is the (b) (4) film of the aluminium bottom foil and the heat seal coating of the lidding foil.

**Review comments:**

- **Moisture sensitivity.** Water vapor transmission testing was conducted on the bottle system per USP <671>, and the compendial criteria were met. The applicant states that dissolution of the product decreases under high humidity conditions. Therefore, the bottle system includes a desiccant to ensure adequate stability during the long term storage and in-use storage. (b) (4)  
(b) (4)  
(b) (4)
- **Safety of the packaging components.** The applicant states that the components (bottle, cotton, blister materials) comply with applicable 21 CFR food additive regulations.
- **Suitability of the packaging components.** The primary stability batches were packaged in the proposed commercial container closure systems (including the physician blister samples).
- **DMFs.** The primary reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral drug products.

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**Stability of the drug product**

Primary Stability

Stability data of 3 primary stability batches of linagliptin film-coated tablets, 5 mg are presented in this section. All primary stability batches tested were manufactured at production-scale according to the proposed commercial manufacturing process and were packaged in the proposed commercial packaging configuration, which are HDPE bottles with desiccant as well as in aluminium / aluminium blisters, intended for physician samples. The design of the stability studies for the primary stability batches for linagliptin film-coated tablets is shown in [Table 23](#).

Table 23 Storage conditions, time points, and test parameters for primary stability testing of linagliptin film-coated tablets

Storage conditions	Storage time (months)							
	0	3	6	9	12	18	24	36
25°C/60 % RH	B	A	A	A	B	A	B	B
40°C/75 % RH		A	A	-	-	-	-	-

Test Parameters:

A: Description

Loss on drying

Dissolution

Degradation products

Assay

B: Description

Loss on drying

Dissolution

Degradation products

Assay

Microbial limits

**Review comments:**

Primary stability data available in the NDA include 18-month at 25 °C/60% RH (long term) and 6-month at 40 °C/75% RH (accelerated) data of the 3 primary batches manufactured at full scale at the commercial facility and packaged in commercial container closure systems (including the physician sample). Therefore, a sufficient amount of stability data is submitted for filing purposes (i.e., there are stability data from product batches of the commercial formulation, manufactured at the commercial site (b) (4) and packaged in the commercial container closure systems). The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.

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**Supporting NDA or IND:**

IND 70963: same sponsor

**Supporting DMF:**

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA
(b) (4)	III		(b) (4)	X
	III			x

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**GMP facilities:**

EER was created and sent to Compliance on 11-JUL-2010 by K. Sharma (ONDQA PM). All sites are ready for inspection.

<b>Drug Substance – Linagliptin</b>	
<b>Establishment and Registration Number</b>	<b>Activity</b>
<b>Boehringer Ingelheim Pharma GmbH &amp; Co. KG</b> Binger Strasse 173 55216 Ingelheim am Rhein GERMANY FEI: 3002806556 DUNS: 551147440	All aspects of the manufacturing (b) (4), packaging, labeling, quality control operations, and stability testing.
Contact: Ricardo Giralt Quality/Group Quality Assurance Boehringer Ingelheim Pharma GmbH & Co.KG Telephone: +496132-772281 Facsimile: +496132-722281 E-mail: <a href="mailto:ricardo.giralt@boehringer-ingelheim.com">ricardo.giralt@boehringer-ingelheim.com</a>	

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<b>Drug Product – Linagliptin Tablets, 5 mg</b>	
<b>Establishment and Registration Number</b>	<b>Activity</b>
<b>Boehringer Ingelheim Roxane, Inc.</b> 1809 Wilson Road Columbus, Ohio 43228 U.S.A. CFN: 1510690 DUNS: 058839929	All aspects of manufacturing, packaging, labeling and testing (release and stability)
Contact: Mark Edmonds Quality Affairs, Boehringer Ingelheim Roxane, Inc. Telephone: (614) 276-4000 x2466 Facsimile: (614) 279-5543 E-mail: <a href="mailto:mark.edmonds@boehringer-ingelheim.com">mark.edmonds@boehringer-ingelheim.com</a>	
<b>Boehringer Ingelheim Roxane, Inc.</b> 330 Oak Street Columbus, Ohio 43215 U.S.A. CFN: 1527529 DUNS: 002655556	Testing
Contact: Mark Edmonds Quality Affairs, Boehringer Ingelheim Roxane, Inc. Telephone: (614) 276-4000 x2466 Facsimile: (614) 279-5543 E-mail: <a href="mailto:mark.edmonds@boehringer-ingelheim.com">mark.edmonds@boehringer-ingelheim.com</a>	
<div style="text-align: right; padding-right: 5px;">(b) (4)</div>	

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**CHEMISTRY NDA FILEABILITY CHECKLIST**

**PRODUCT QUALITY**  
**FILING REVIEW FOR NDA (ONDQA)**

NDA Number: 201280

Established/Proper Name:  
linagliptin

Applicant: Boehringer  
Ingelheim  
Pharmaceuticals Inc.

Letter Date: 02-JUL-2010

Stamp Date: 02-JUL-2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			

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7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		

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9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	x		

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<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

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<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	x		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	

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*{See appended electronic signature page}*

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Su (Suong) Tran  
CMC Lead  
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

*{See appended electronic signature page}*

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Ali Al Hakim  
Branch Chief  
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201280	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	Linagliptin (BI 1356) Tablets.

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

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/s/

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SUONG T TRAN  
08/09/2010

ALI H AL HAKIM  
08/09/2010