CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 206073/000	**Sponsor:**	BOEHRINGER INGELHEIM
Or Code:	510		900 RIDGEBURY RD
	4		RIDGEFIELD, CT 06877
Stamp Date:	30-JAN-2014	**Brand Name:**	EMPAGLIFLOZIN AND LINAGLIPTIN TABLETS
PDUFA Date:	30-JAN-2015	**Estab. Name:**	EMPAGLIFLOZIN AND LINAGLIPTIN TABLETS
Action Goal:		**Generic Name:**	LINAGLIPTIN
District Goal:	30-AUG-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET; LINAGLIPTIN; 5MG 001; TABLET; EMPAGLIFLOZIN; 10MG 002; TABLET; LINAGLIPTIN; 5MG 002; TABLET; EMPAGLIFLOZIN; 25MG

FDA Contacts:				
	J. LEGINUS	Prod Qual Reviewer	(HFD-810)	3017964102
	E. PFEILER	Micro Reviewer	(HF-22)	3017960642
	P. KUMAR	Product Quality PM	(HFD-800)	2404023722
	C. CAPPEL-LYNCH	Regulatory Project Mgr		3017938436

Overall Recommendation: ACCEPTABLE on 22-JUL-2014 by R. SAFAAI-JAZI () 3017964463

Establishment: **CFN:** 9610492 **FEI:** 3002306556

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
BINGER STREET 173

INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY

DMF No: AADA:

nsibilities: FINISHED DOSAGE MANUFACTURER

e: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 1510690 **FEI:** 1510690

BOEHRINGER INGELHEIM ROXANE INC

COLUMBUS, , UNITED STATES 432289579

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-FEB-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-FEB-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN:	FEI: (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-FEB-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN:	FEI: (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-FEB-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-JUL-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Milestone: OC RECOMMENDATION

Milestone Date: 12-FEB-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

/s/

MARY GRACE LUBAO
02/09/2015

NDA 206073

Glyxambi®
(Empagliflozin/Linagliptin) Tablet

Boehringer Ingelheim Pharmaceuticals, Inc.

Joseph Leginus, PhD
Office of New Drug Quality Assessment
Division III, Branch VII

For the Division of
Metabolism and Endocrinology Products

CHEMISTRY REVIEW #1

Table of Contents

Chemistry Review Data Sheet

1. NDA 206073

2. REVIEW #: 1

3. REVIEW DATE: 19-Aug-2014

4. REVIEWER: Joseph Leginus, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	30-Jan-2014
Amendment	24-Jun-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc
Address:	900 Ridgebury Road, PO Box 368 Ridgefield, CT 06877
Representative:	Chung Lee-Sogaard Associate Director, Regulatory Affairs
Telephone:	203-798-4224

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Glyxambi
b) Non-Proprietary Name (INN): Empagliflozin/Linagliptin
c) Code Name/# (ONDC only): Empagliflozin/Linagliptin Film-coated Tablets
Type/Submission Priority (ONDC only):

- Chem. Type: 4 (New combination)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.

10. PHARMACOL. CATEGORY:

Empagliflozin is an inhibitor of the sodium-dependent glucose cotransporter 2 (SGLT-2), the major transporter responsible for renal glucose reabsorption; Linagliptin is an inhibitor of the enzyme dipeptidyl peptidase 4 (DPP-4) for use in the treatment of type 2 diabetes mellitus.

11. DOSAGE FORM: Immediate release tablet (Film-Coated)

12. STRENGTH/POTENCY:

Empagliflozin/Linagliptin tablets are manufactured in two strengths: 10 mg/5 mg and 25 mg/5 mg represented as empagliflozin mg/linagliptin mg.

13. ROUTE OF ADMINISTRATION: Oral

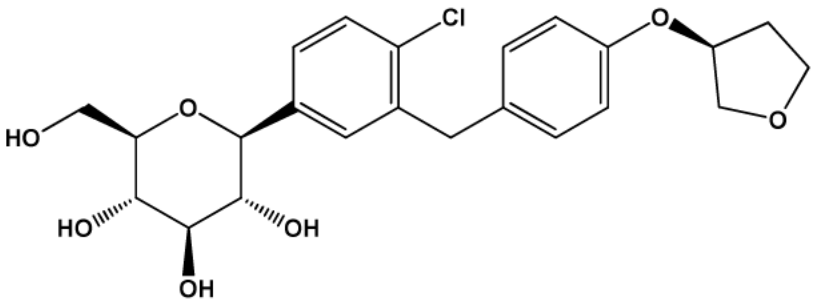
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

_____SPOTS product – Form Completed
__x___Not a SPOTS product

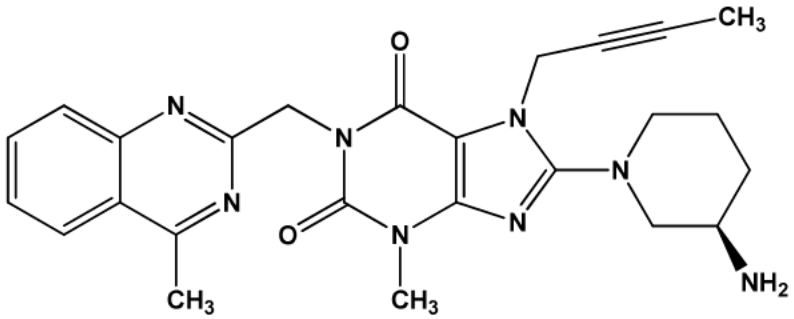
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

A. Empagliflozin
Chemical Name: D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S)
Structural Formula:



Molecular Formula: $C_{23}H_{27}ClO_7$
Molecular Weight: 450.91 g/mol

B. Linagliptin
Chemical Name: 8-[(3*R*)-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.
Structural Formula:



Molecular Formula: $C_{25}H_{28}N_8O_2$
Molecular Weight: 472 (b) (4) g/mol
Chirality: One chiral center (R conformation).

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed
(b) (4)	III	(b) (4)		3	Adequate	14-Dec-2012
	III			3	Adequate	15-Jun-2012
	III			3	Adequate	10-Sep-2012
	III			3	Adequate	12-Mar-2013
	III			3	Adequate	17-Apr-2012

[1] 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")

[2] 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	108388	Empagliflozin/Linagliptin Tablet[1]
NDA	204629	Empagliflozin Tablet[1]
NDA	201280	Tradjenta® (linagliptin) Tablet[1]

[1]Applicant/Sponsor is Boehringer Ingelheim

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	An Overall Compliance recommendation of Acceptable has been provided.	22-Jul-2014	N/A
Pharm/Tox	N/A. Impurity degradants are below ICH qualification thresholds.		
Biopharm	Biopharmaceutics evaluation of dissolution data.	Pending	Kareen Riviere
Methods Validation	Not required. No novel methods.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	19-Aug-2014	Joseph Leginus
Microbiology	Recommended for approval from the standpoint of product quality microbiology.	8-Aug-2014	Erika Pfeiler

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 206073

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from a CMC perspective is Approval, pending:

A recommendation from Biopharmaceutics regarding adequacy of dissolution testing of the drug product, currently pending.

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

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCES

Glyxambi is a combination product containing two drug substances: empagliflozin and linagliptin.

Empagliflozin
Empagliflozin (an NME) is described in NDA 204629 for empagliflozin tablets which received a Complete Response on 3/4/2014. This was due to a Withhold recommendation from the Office of Compliance following an inspection at the Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany drug substance/drug product manufacturing plant. NDA 204629 was approved on Aug 1, 2014 after an overall cGMP recommendation was made by the Office of Compliance upon resubmission of the NDA. Information for empagliflozin is provided in the sponsor's NDA 204629 and is incorporated by reference herein.

Linagliptin

The drug substance linagliptin is described in NDA 201280 for Tradjenta® (linagliptin) tablet which was approved on May 2, 2011. Information for linagliptin is provided in the Applicant's approved NDA 201280 and is incorporated by reference herein.

DRUG PRODUCT

Glyxambi (empagliflozin/linagliptin) tablet is formulated as a fixed-dose combination, immediate-release, film-coated tablet for oral administration containing two drug substances, empagliflozin and linagliptin. Two dosage strengths have been developed containing two levels of empagliflozin (10 mg or 25 mg) and a fixed amount of linagliptin (5 mg). The two tablets are identical in shape (arc triangular, flat faced, bevel-edged film-coated tablets) but are distinguished by color and debossing. The 10 mg/5 mg tablets are pale yellow and one side is debossed with "10/5" while the 25 mg/5 mg tablets are pale pink and one side is debossed with "25/5". Total weight for each strength tablet is 185 mg.

The two strength tablets are formulated with the same excipients in slightly differing amounts. Excipients including mannitol, pregelatinized starch, corn starch, copovidone, crospovidone, magnesium stearate and talc are part of the tablet core. The film coat is based on (b) (4) Yellow (10 mg/5 mg) and (b) (4) (25 mg/5 mg) mixtures which consist of hypromellose (b) (4), mannitol, titanium dioxide, talc, polyethylene glycol (b) (4) and ferric oxide yellow and red, respectively. No novel excipients are used to manufacture empagliflozin/linagliptin tablets. All excipients have compendial references and are identified in FDA's Inactive Ingredients Database as inactive ingredients found in other oral tablet products at levels higher than those described above for empagliflozin/linagliptin tablets.

Empagliflozin/linagliptin tablets are manufactured (b) (4) Tablets are packaged in a) high density polyethylene plastic bottles (60 cc and 375 cc) containing 30, 90 or 1000 tablets, and b) aluminum- (b) (4) blisters containing 10 tablets.

The proposed release specifications include description (visual), identification (HPLC and UV), degradation products (HPLC), assay (HPLC), content uniformity, disintegration, and microbiological quality. Batch analysis data from 8 clinical and stability lots manufactured at commercial scale at the proposed site for commercial production show that the drug products meet the specifications proposed.

Results from stability studies show that empagliflozin/linagliptin tablets packaged in either HDPE bottles or blister packs remain stable through a) 12 months at the long-term storage condition of 25°C/60% RH, and b) 6 months at the accelerated condition of 40°C/75% RH. The drug product also demonstrates good stability when exposed to

ambient and high humidity conditions for longer than the in-use period. Photostability studies indicate no effect on the product due to exposure to light. Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 24 months is granted for empagliflozin/linagliptin tablets 10 mg/5 mg and 25 mg/5 mg when maintained at 25°C/60% relative humidity in the proposed container closure systems. This is in agreement with the Applicant's proposed expiry period for the drug product.

Boehringer Ingelheim requested a categorical exclusion from submitting an environmental assessment for the drug product empagliflozin/linagliptin tablets based on the regulations in 21 CFR, part 25, section 25.31(b). The request is granted.

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

Glyxambi combines two antihyperglycemic agents (empagliflozin and linagliptin) with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes.

Empagliflozin is an inhibitor of the sodium-dependent glucose cotransporter 2 (SGLT-2). SGLT-2 accounts for about 90 percent of glucose reabsorption into the blood. Therefore, an SGLT-2 inhibitor such as empagliflozin may be effective at reducing blood glucose levels by blocking glucose reabsorption in the kidney and allowing glucose to be excreted in the urine.

Linagliptin is an orally-active 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.

Empagliflozin/linagliptin is formulated as an immediate-release tablet for once-daily oral administration. The recommended starting dose is 10 mg/5 mg. The dose may be increased to 25 mg/5 mg in patients who require additional glycemic control.

C. Basis for Approvability or Not-Approval Recommendation

This is a 505(b)(1) application where one of the two drug substances, empagliflozin, is a New Molecular Entity (NME). Information for the drug substances, empagliflozin and linagliptin are provided in the Applicant's NDA 204629 for Empagliflozin tablets (recommended for approval from a CMC perspective) and their approved NDA 201280 for Tradjenta® (linagliptin) tablets, respectively.

The drug product will be manufactured as immediate-release tablets at the Boehringer Ingelheim Pharma facility in Ingelheim am Rhein, Germany. Drug product specifications include attributes standard for this type of dosage form. Limits on degradation products

are within applicable ICH thresholds. Eight clinical and stability lots have been manufactured at commercial scale at the proposed site for commercial production with each lot meeting the specifications proposed. Stability of the drug product has been adequately established in the two container closure systems, HDPE bottles and blister packs to grant a shelf-life of 24 months when stored at controlled room temperature.

The risk from a safety perspective for this combination drug product is anticipated to be low since each drug substance in empagliflozin/linagliptin is an active ingredient in two of the Applicant's previously submitted drug products at similar strengths: NDA 204629 for Empagliflozin tablets (recommended for approval from a CMC perspective) and the approved NDA 201280 for Tradjenta® (linagliptin) tablets, respectively.

ONDQA Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product Attribute/ CQA	**Factors That Can Impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	• Formulation • Container Closure • Raw Materials • Process • Parameters • Scale/Equipment • Site	L	Empagliflozin- and Linagliptin-related impurities in accordance with the ICH Q3B(R2).	Acceptable	Linagliptin-related Single Impurity > (b) (4)%
Physical Stability (solid state)	• Formulation • Container Closure • Raw Materials • Process • Parameters • Scale/Equipment • Site	L	Empagliflozin – no polymorphs. Linagliptin – two polymorphs. (b) (4)	Acceptable	Both APIs: (b) (4) BCS III.
Content Uniformity	• Formulation • Container Closure • Raw Materials • Process • Parameters • Scale/Equipment • Site	L	(b) (4)	Acceptable	(b) (4) (b) (4)
Microbial Limits	See Risk Assessment by the Microbiology reviewer.				

Dissolution	See Risk Assessment by the Biopharmaceutics reviewer.				
Other CQAs	--	--	--	--	--

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

Acceptable cGMP recommendations have been received from the Office of Compliance for all manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 22-Jul-2014.

A recommendation for approval from the standpoint of product quality microbiology was provided on 08-Aug-2014.

At this time, recommendations from Biopharmaceutics regarding adequacy of dissolution testing of the drug product.

III. Administrative

A. Reviewer's Signature: in DAARTS.

B. Endorsement Block: in DAARTS.

C. CC Block: in DAARTS.

58 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

JOSEPH LEGINUS
08/19/2014

DANAE D CHRISTODOULOU
08/19/2014
I concur with the reviewer's conclusions and recommendation

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206073

2. DATES AND GOALS:

Letter Date: 29-JAN-2014	Submission Received Date : 30-JAN-2014

PDUFA Goal Date: 30-JAN-2015

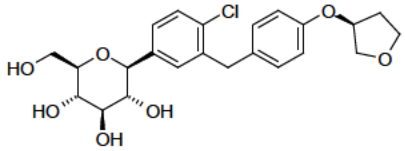
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Not yet finalized
Established Name (USAN):	Empagliflozin/linagliptin
Dosage Form:	Tablet
Route of Administration	Oral
Strength/Potency	10/5 and 25/5 mg/mg empagliflozin/linagliptin
Rx/OTC Dispensed:	Rx

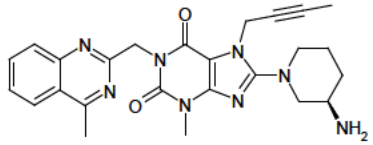
4. INDICATION: Treatment of type 2 diabetes

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Empagliflozin
D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S)
$C_{23}H_{27}ClO_7$
450.91 g/mol



Linagliptin
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]-
$C_{25}H_{28}N_8O_2$
472.54 g/mol



6. NAME OF APPLICANT (as indicated on Form 356h): Boehringer Ingelheim

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code)	4
Application Type	505(b)(1)
Breakthrough Therapy	No

Responsible Organization (Clinical Division)	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS:
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		To be sent by ONDQA-PM
Pharmacology/Toxicology		x	Impurity degradants are below ICH qualification thresholds.
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment		x	Categorical exclusion request to be reviewed by Primary Reviewer
CDRH		x	

Does the submission contain any of the following elements? No			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes - One CMC reviewer and one Biopharmaceutics reviewer are needed to review the drug product information of the new NDA. Reference is made to the approved NDA 201280 (linagliptin) and the pending NDA 204629 (empagliflozin) for all CMC information on the drug substances.

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No

Biopharmaceutics: See the Biopharmaceutics filing review attached at the end of this IQA.

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes 1. Provide supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). 2. Submit SAS Transport files of the pharmacokinetic data from the BE study. The data should include AUC0-t, AUC0-inf, Cmax, Tmax, Kel, and T1/2 as shown. Please submit the data in the following format: SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf

Microbiology: See Microbiology Filing Review in DARRTS for details and for any potential Microbiology review issues.

Summary of Critical Issues and Complexities

Previous quality-related meeting between ONDQA and the sponsor:
Comments from FDA's letter dated 14-AUG-2013:

Does the Division have any comments about the proposed approach for Module 3 and QOS of the empagliflozin + linagliptin FDC NDA?

FDA Pre-Meeting Response

We agree with your proposed Module 3 sections and QOS of the new NDA. We remind you to include in the NDA a complete list of all testing and manufacturing facilities used for the drug substances and drug product in Form 356h of the NDA, with detailed contact information and a statement that all facilities are ready for the GMP inspection at the time of the NDA submission.

Question 4

The single entity tablets empagliflozin and linagliptin that were used in the pivotal safety and efficacy Study 1275.1 and the relative bioavailability Study 1275.3 are equivalent formulations to the to-be-marketed empagliflozin 10 and 25 mg tablets described in NDA 204629 (submitted March 5, 2013) and to the marketed TRADJENTA 5 mg tablets described in NDA 201280 (approved May 2, 2011). At the start of study 1275.1, the empagliflozin + linagliptin FDC tablets in Study 1275.1 were (b) (4) to the empagliflozin + linagliptin FDC tablets used in the bioavailability Study 1275.3, which supports equivalence of the FDC to its components. During the 1275.1 trial, there was a minor change to the quantitative composition of the FDC tablets (b) (4) (b) (4) in the FDC tablets when compared to the FDC tablets used in 1275.3 and first used in trial 1275.1. This change was not deemed to impact the bioavailability of the active components. Considering these data, BI believes that reference to the NDAs for the individual drug products to support safety and efficacy of empagliflozin and linagliptin is appropriate. Does the Division concur with BI's approach?

FDA Pre-Meeting Response

Biopharmaceutics:

This submission did not include a comparative qualitative and quantitative composition of the FDC formulation for the pre- and post change. However, based on the percent change mentioned in the question above, this manufacturing change could be considered minor requiring dissolution profiles comparisons. Therefore, to support the bridging of these formulations, provide the following information in the NDA submission:

1. Comparative qualitative and quantitative composition of the FDC formulation for both strengths of your product for the pre- and post change.
2. Comparative dissolution data using the regulatory dissolution method for each FDC tablet strength manufactured pre- and post- the proposed changes. Also, provide individual (n=12), mean, minimum, maximum, RSD, profile data, and calculate the similarity factor f2 values.

Additional Biopharmaceutics Comments

General comments to consider for information expected at the time you plan to submit your proposed dissolution method:

1. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.
2. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).
3. Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.
4. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e. specification-sampling time point and specification value) for both components of the proposed product.
5. Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

6. Per CFR §320.22 and the Guidance for Industry "Bioavailability and Bioequivalence Studies for Orally Administered Drug Product – General Considerations", the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the bioequivalence of the lower strength (10 mg empaglifolzin/5 mg linagliptin) can be waived if you submit a biowaiver request and meet the following criteria:

    - The lower strength is compositionally proportional in its active and inactive ingredients to the higher strength.
    - Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements.
    - There is BA/BE data for the highest strength.

BI Pre-Meeting Response and Question:

Regarding the specification for dissolution (Biopharmaceutics Additional Comments 4 and 5), BI will include a disintegration test in the specification for the drug product in lieu of dissolution. Data will be presented in the NDA supporting this choice based on decision tree #7 of ICH Q6A.

Is this proposal acceptable?

FDA Additional Pre-Meeting Comments regarding BI's Response and Question

Yes, your proposal is acceptable. The following supportive information/data described in the ICH Topic Q6A document should be provided in the NDA to support your proposal of using the disintegration test in lieu of the dissolution test:

a. Solubility profiles for the drug substance throughout the physiological pH range (1.2 to 6.8).
b. Dissolution profiles of the proposed drug product at pH 1.2, 4.0 and 6.8.
c. Data showing a relationship between dissolution and disintegration or data showing that disintegration is more discriminating than dissolution.
d. The complete development and validation data for the dissolution method.
e. Information on the formulation and process factors that may impact dissolution/ disintegration (i.e., amount of disintegrant, surfactant, and lubricant).

Since our recommendation regarding the acceptability of using disintegration instead of dissolution is a review issue under the NDA, you should include complete dissolution as well as disintegration data in your NDA submission. Additionally, note that a dissolution method should be available for your product to support future SUPAC changes under post-approval supplements.

FDA concurred with BI's response. BI agreed to provide the additional information described above at the time of NDA submission. Agreement was reached on this issue.

Drug Substance

The drug substance empagliflozin is described in NDA 204629 (submitted March 5, 2013) for empagliflozin film-coated tablets, which is currently under review. The drug substance linagliptin is described in NDA 201280 for linagliptin film-coated tablets, for which marketing authorization was granted (approved May 2, 2011). Both drug substances are therefore not covered in Module 3 for empagliflozin / linagliptin film-coated tablets or in this Quality Overall Summary.

Drug Product

The film-coated tablets consist of immediate release empagliflozin and immediate release linagliptin with the strengths of 10/5 and 25/5 mg/mg (empagliflozin/linagliptin).

Composition. (see the copied composition table at the end of this review) There is no novel excipient. Magnesium stearate (b) (4)

Comparability of the product used in the clinical studies, stability studies, and commercial product. Product batches 108244 (10/5 mg/mg) and 108247 (25/5 mg/mg) were used in the pivotal clinical study 1275.1. These batches have the commercial formulation and were manufactured at the commercial site/scale, packaged in the commercial container/closure systems. They are submitted as primary stability batches in the NDA.

Product manufacture. (b) (4)

Drug product specification. (see the copied specification at the end of this review)
The drug product specification includes attributes standard for this type of dosage form. Limits on degradation products are within applicable ICH thresholds. Only two degradants are found above the ICH reporting threshold during the stress and primary stability studies (copied below). Limits on both degradants are within applicable ICH qualification thresholds.

(b) (4) is the major degradation product of the active ingredient linagliptin observed in empagliflozin / linagliptin film-coated tablets. This impurity is derived from linagliptin by (b) (4) The structure is shown in Figure 12.

(b) (4)

(b) (4) is the major degradation product of the active ingredient empagliflozin observed in empagliflozin / linagliptin film-coated tablets. This impurity is the (b) (4) (b) (4) The structure is shown in Figure 11.

(b) (4)

All dissolution-related information, including disintegration, will be evaluated by the ONDQA Biopharmaceutics team. Of the several attributes omitted from the drug product specification, these two specific omissions will be evaluated by the reviewer: (b) (4) (claimed by the applicant not to be a Critical Quality Attribute because it (b) (4) , and enantiomeric purity (claimed by the applicant to undergo no change during stress stability of the product).

Container closure systems. The drug product will be packaged in HDPE bottles and aluminum blisters. The applicant states that the safety of the product-contact packaging components is shown by compliance to the indirect food additives. Applicable USP testing per <671> for water vapor transmission was conducted. Compatibility is shown by stability data supporting both packaging systems. The reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral dosage form drug products.

Stability. Sufficient stability data are provided in the submission for filing. The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data. For the six product batches (3 of each strength) manufactured by the commercial process/site/scale: Stability data are provided for 12 months at 25 °C/60% RH, and 30 °C/75% RH and for 6 months at 40 °C/75% RH. Additional data are provided for the stress studies (heat, humidity, and photostability).

Comparability protocol. None proposed.

FILING REVIEW CHECKLIST

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*				
*****	**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.**			
	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? **This question is not applicable for synthesized API.**	x		
	Parameter	**Yes**	**No**	**Comment**
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D.	DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)			
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		Reference is made to the approved NDA 201280 (linagliptin) and the pending NDA 204629 (empagliflozin).
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	

E.	DRUG PRODUCT (DP)			
	Parameter	**Yes**	**No**	**Comment**
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.	Has any biowaiver 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	

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			Not applicable.

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		

DMF#	TYPE	HOLDER	ITEM REFERENCED	LOA DATE
(b) (4)	III	(b) (4)		11-JAN-2013
	III			29-JUL-2010
	III			11-JAN-2013
	III			02-JAN-2013
	III			18-DEC-2012

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		

See appended electronic signature page}

2.3.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Empagliflozin / linagliptin film-coated tablets, 10 mg/5 mg are pale yellow, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol, the other side is debossed with "10/5".

Empagliflozin / linagliptin film-coated tablets, 25 mg/5 mg are pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol, the other side is debossed with "25/5".

The composition of the drug product is provided in Table 2 below.

Table 2 Composition of empagliflozin / linagliptin film-coated tablets, 10 mg/5 mg and 25 mg/5 mg

Ingredient	Dosage strength		Function	Reference to Standards
	10 mg/5 mg	25 mg/5 mg		
Tablet core	[mg/tablet]		--	
Empagliflozin	10.00	25.00	Drug substance	Company standard
Linagliptin	5.00	5.00	Drug substance	Company standard
Mannitol	(b) (4)			USP
Pregelatinized starch				NF
Corn starch				NF
Copovidone				NF
Crospovidone				NF
Talc				USP
Magnesium stearate				NF
(b) (4)				USP
Film coat	[mg/tablet]		--	
(b) (4)				Company standard
				Company standard
				USP
Total film-coated tablet	185.0	185.0	--	--

(b) (4)

(b) (4)

(b) (4)

Table 3 Composition of [redacted] film coat

Ingredient	[redacted]		Function	Reference to Standards
--	[mg/tablet]	[mg/tablet]	--	
Hypromellose [redacted]	[redacted]			USP
Mannitol				USP
Talc				USP
Titanium dioxide				USP
Polyethylene glycol [redacted]				NF
Ferric oxide, yellow				NF
Ferric oxide, red				NF
Total	5.00	5.00	--	--

Table 16 Specification for empagliflozin / linagliptin film-coated tablets

Test parameter	Method	Acceptance criteria
Description	Visual Test	For the 10 mg/5 mg dosage strength: Pale yellow, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol, the other side is debossed with "10/5". For the 25 mg/5 mg dosage strength: Pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol, the other side is debossed with "25/5".
Disintegration	Physical test	≤ (b) (4) min Complies with Ph.Eur./USP/JP
Identification – Empagliflozin Linagliptin	Liquid chromatography	For each active ingredient: The retention time of the active ingredient obtained with the test solution must correspond to that obtained with the standard solution. The UV spectrum of the active ingredient obtained with the test solution must correspond to that obtained with the standard solution.
Active Ingredient Degradation – Empagliflozin	Liquid chromatography	(b) (4) ≤ (b) (4) % Any unspecified degradation product ≤ % Total degradation products ≤ %
Active Ingredient Degradation – Linagliptin	Liquid chromatography	(b) (4) ≤ (b) (4) % Any unspecified degradation product ≤ % Total degradation products ≤ %
Assay – Empagliflozin Linagliptin	Liquid chromatography	For each active ingredient: (b) (4) % of stated content
Uniformity of dosage units – Empagliflozin Linagliptin	Liquid chromatography	For each active ingredient: Requirement Acceptance value A (n=10) ≤ (b) (4) % B (n=30) ≤ %, no individual value is less than (b) (4) M nor more than (b) (4) M Complies with Ph.Eur./USP/JP
Microbiological quality	Standard test Ph. Eur./USP/JP	Total aerobic microbial count (TAMC)/g ≤ (b) (4) cfu Total combined yeasts/moulds count (TYMC)/g ≤ cfu Escherichia coli/g absent Skip lot testing (b) (4) production batch per year