CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208026Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

Filing Meeting: September 9, 2015
NDA 208026
Drug: Linagliptin and metformin hydrochloride (HCl) extended-release (XR) fixed dose combination (FDC)
Sponsor: Boehringer Ingelheim (BI)
Date Received: July 27, 2015
PDUFA date: May 27, 2016

Assessment: From the clinical standpoint, the NDA is fileable.

Background:

This is a 505(b)(1) NDA for linagliptin and metformin hydrochloride XR FDC tablets for once daily administration in patients with type 2 diabetes mellitus (T2DM). The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate.

The sponsor cross-referenced the existing clinical safety and efficacy data for linagliptin (Trajenta; NDA 201280), combination of linagliptin and metformin HCl immediate release (Jentadueto; NDA 201281), and metformin XR (Glumetza; NDA 021748). BI is the NDA holder for both Tradjenta and Jentadueto and has obtained a right of reference and full access to use the information included within Glumetza NDA.

The sponsor intends to market two strengths of linagliptin/metformin XR FDC tablets, 2.5 mg/1000 mg and 5 mg/1000 mg. To bridge the efficacy and safety data from three referenced NDAs to this FDC, the sponsor submitted results from two pivotal clinical pharmacology studies to demonstrate the bioequivalence (BE) between linagliptin/metformin XR FDC tablet strengths 5/1000 mg and 2.5/1000 mg to the co-administration of individual components in Study 1288.9 and Study 1288.11, respectively.

The sponsor did not submit Integrated Summary of Efficacy or Integrated Summary of Safety (ISS) as only Phase 1 studies have been conducted for this NDA. In lieu of ISS, the sponsor provided the most recent Periodic Benefit Risk Evaluation Report (Date of report June 30, 2015; covering May 3, 2014 to May 2, 2015) for Jentadueto in Module 5.3.6 to provide updated safety information related to combined use of linagliptin and metformin. This is in agreement with our pre-NDA meeting responses.

We agreed with sponsor's Agreed Initial Pediatric Study Plan on June 12, 2015.

NDA/BLA Number: 208026 **Applicant: Boehringer Ingelheim** **Stamp Date: July 27, 2015**

Drug Name: linagliptin and metformin hydrochloride extended release **NDA/BLA Type: 505(b)(1)**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Sponsor submitted Clinical Overview in Module 2.5 as requested; we agreed that Clinical summaries are not required for Module 2.7
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		Not needed for this NDA
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		Not needed for this NDA
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			In Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to			X	

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study – BE studies Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate			X	The basis for the submission is a bioequivalence study.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	Efficacy for combined linagliptin and metformin use was previously reviewed in Jentadueto NDA (201281)
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			Submitted recent Periodic Benefit Risk Evaluation Report
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
26.	Has the applicant submitted the coding dictionary[2] used for	x			MedDRA Version

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

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				16.0 was used for reporting Study 1288.8; Version 17.0 was used for reporting 1288.9, 1288.10, and 1288.11.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			CRFs and narratives for SAEs and discontinuations due to AEs from Phase 1 studies submitted as requested
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	None requested from clinical
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			iPSP agreed on June 12, 2015
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			In Clinical Overview
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				Defer to Clin Pharm
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?				Defer to Clin Pharm
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				Defer to Clin Pharm
37.	Are all datasets to support the critical safety analyses available and complete?				Defer to Clin Pharm
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				Defer to Clin Pharm
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			All clinical investigators listed for BE studies are employees of BI
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

The application is fileable pending Clinical Pharmacology review of the datasets submitted.

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

- The hyperlinks to the safety narratives for subjects with serious adverse events and adverse events leading to discontinuation from Phase 1 studies provided in Table 5.4: 3 of Clinical Overview are not correctly linked to narratives. Please resubmit the table with correct hyperlinks to facilitate review.

Hyon (KC) Kwon — September 24, 2015
Reviewing Medical Officer — Date

Lisa Yanoff — September 24, 2015
Clinical Team Leader — Date

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

/s/

HYON J KWON
09/24/2015

LISA B YANOFF
09/24/2015

CLINICAL REVIEW

Application Type	505 (b)(1)
Application Number(s)	NDA 208026
Priority or Standard	Standard
Submit Date(s)	July 27, 2015
Received Date(s)	July 27, 2015
PDUFA Goal Date	May 27, 2016
Division / Office	DMEP/ODE 2
Reviewer Name(s)	Hyon J. Kwon
Review Completion Date	May 17, 2016
Established Name	Linagliptin/metformin HCL
(Proposed) Trade Name	Jentadueto XR
Therapeutic Class	DPP4 inhibitor and biguanide
Applicant	Boehringer Ingelheim
Formulation(s)	Linagliptin/metformin HCL ER FDC oral tablets at dosages of 5 mg/1000 mg, 2.5 mg/1000 mg
Dosing Regimen	Once daily
Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin

	and metformin is appropriate
Intended Population(s)	Adults with type 2 diabetes mellitus

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1 Recommendations/Risk Benefit Assessment

This document contains the clinical efficacy and safety review for NDA 208-026 which seeks approval of a new linagliptin and metformin extended release fixed-dose combination product (linagliptin/metformin XR) for the treatment of patients with type 2 diabetes mellitus. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate

1.1 Recommendation on Regulatory Action

I recommend **approval** of linagliptin/metformin XR for the proposed indication.

1.2 Risk Benefit Assessment

The Applicant is seeking approval of two strengths of the linagliptin/metformin XR FDC where one or two tablets are to be administered once daily with a meal, as follows:

- Linagliptin/metformin HCl XR 5 mg/1000 mg; one tablet to be given once daily with a meal;
- Linagliptin/metformin HCl XR 2.5 mg/1000 mg; two tablets to be given once daily with a meal (providing total daily dose of 5 mg of linagliptin and 2000 mg of metformin HCL XR).

The clinical efficacy and safety of individual components in the proposed FDC, linagliptin and metformin XR, have already been established in the Tradjenta (201-280) and Glumetza (021-748) NDA, respectively. The efficacy and safety of linagliptin as add-on to metformin therapy have been previously established in the Tradjenta NDA. In addition, the efficacy and safety of co-administration of linagliptin and metformin immediate release (IR) twice daily compared to individual component have been established in Jentadueto NDA (201-281) from the factorial design study. Also, the efficacy and safety of once daily metformin XR was comparable to metformin IR twice daily in Glumetza NDA.

Therefore, the clinical development for the proposed linagliptin/metformin XR FDC product was designed to bridge the existing clinical efficacy and safety data by demonstrating bioequivalence (BE) of each FDC tablet to the free combinations of the individual components co-administered in healthy volunteers in Phase 1 BE studies. The pivotal BE studies (Study 1288.9 and 1288.11) demonstrated that both proposed strengths of the linagliptin/metformin XR FDC were bioequivalent to the combination of individual components under both fasted and fed conditions.

The safety review of these Phase 1 BE studies or postmarketing safety data was based on review of narratives for all subjects who discontinued from the Phase 1 studies due to adverse events and who had serious adverse events, most recent postmarketing safety data submitted with the application, and data from the 4-month safety update. The safety review did not identify any new safety issues with use of the combination. We would expect the safety of linagliptin/metformin XR FDC product be similar to Jentadueto.

Therefore, the benefit risk profile of linagliptin and metformin XR FDC is favorable for approval.

It is generally believed that fixed-dose combinations have the potential to improve adherence to therapy by reducing the number of pills needed and simplifying the dosing regimen. In theory, once daily FDC would also reduce dosing frequency and may increase treatment adherence. The NDA for linagliptin/metformin XR did not provide any data to assess adherence; however, I do not believe that these data are needed for an approval recommendation.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

This is a new NDA submitted for the fixed-dose combination (FDC) of linagliptin and metformin extended release (XR) for the treatment of adults with type 2 diabetes mellitus (T2DM). The proposed indication is an adjunct to diet and exercise to improve glycemic control in adults with T2DM in whom treatment with both linagliptin and metformin hydrochloride is appropriate.

2.1 Product Information

Linagliptin (Tradjenta) is a dipeptidyl peptidase-4 (DPP-4) inhibitor, and prevents the degradation of incretin hormones such as glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). It was approved for the treatment of T2DM in the U.S. on May 2, 2011 (NDA 201-280). The recommended dose of linagliptin is 5 mg once daily with or without food.

Metformin is an oral biguanide, which decreases production of hepatic glucose and improves insulin sensitivity. It was approved for the treatment of T2DM in the U.S. as Glucophage on March 3, 1995 (NDA 20-357). There is no fixed dosage regimen for metformin as it is to be individualized on the basis of effectiveness and tolerance while not exceeding the maximum recommended daily doses. The maximum recommended dose of Glumetza is 2000 mg once daily with food.

Jentadueto, the FDC of linagliptin/metformin immediate release (IR), was approved for the treatment of T2DM in the U.S. on January 30, 2012 (NDA 201-281).

There are varying drug-delivery systems for metformin extended-release (XR) formulations, such as hydrophilic polymer matrix system (e.g., Glucophage XR), single-composition osmotic technology (e.g., Fortamet), and (b) (4) polymer-based system (e.g., Glumetza). The drug delivery system for this FDC NDA is based (b) (4)

2.2 Currently Available Treatments for Proposed Indications

T2DM can be treated with a combination of proper diet, exercise, and the following drug therapies, either alone or in combination:

- Biguanides: metformin (e.g., Glucophage)
- Sulfonylureas (SUs): glyburide (Micronase), glipizide (Glucotrol), glimepiride (Amaryl), chlorpropamide (Diabinese), tolazamide (Tolinase)
- Insulin
- Glucagon-like peptide-1 (GLP-1) agonists: exenatide (Byetta, Bydureon), liraglutide (Victoza), albiglutide (Tanzeum), dulaglutide (Trulicity)
- Thiazolidinediones (TZDs): rosiglitazone (Avandia), pioglitazone (Actos)
- Dipeptidyl peptidase 4 (DPP-4) inhibitors: sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin (Nesina)
- Meglitinides: repaglinide (Prandin), nateglinide (Starlix)
- SGLT2 inhibitors: empagliflozin (Jardiance), dapagliflozin (Farxiga)
- α-Glucosidase inhibitor: acarbose (Precose), miglitol (Glyset)
- Pramlintide (Symlin)
- Dopamine agonist: bromocriptine mesylate (Cycloset)
- Bile acid sequestrants: colesevelam (WelChol)
- Various fixed dose combinations of oral therapies (e.g., Janumet, ActoPlus Met, Kombiglyze XR, Oseni, Kazano)

T2DM is a heterogeneous disease in both pathogenesis and clinical manifestations. Despite the number of treatment options currently available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-hyperglycemic agent (AHA). Many of these drug classes may not

be well-tolerated or have safety issues. For example, SUs and insulins are associated with a higher risk for hypoglycemia, metformin and GLP-1 agonists are associated with gastrointestinal adverse experiences which can limit dose, while metformin and SGLT2 inhibitors are contraindicated in patients with severe renal impairment. Furthermore, progressive beta-cell dysfunction may lead to secondary treatment failure with an anti-diabetic regimen over time requiring the addition of other AHAs. For these reasons, there continues to be a need for treatment options to improve glycemic control in patients with T2DM.

2.3 Availability of Proposed Active Ingredient in the United States

Linagliptin (NDA 201-280) and metformin (Glucophage, NDA 020-357) have been approved for the treatment of T2DM in the U.S. since May 2, 2011 and March 3, 1995, respectively. Jentadueto was approved in the U.S. on January 30, 2012.

2.4 Important Safety Issues With Consideration to Related Drugs

At this time, three other DPP-4 inhibitors aside from linagliptin are currently approved in the U.S. (sitagliptin, saxagliptin, and alogliptin). Safety concerns related to DPP-4 inhibitors as a class include the following:

- Hypersensitivity such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria;
- Pancreatitis;
- Hypoglycemia when used with insulin or insulin secretagogue;
- Severe and disabling arthralgia;
- Heart failure for products containing saxagliptin and alogliptin.

Labeled safety concerns with metformin include the following:

- Lactic acidosis: the risk increases with sepsis, dehydration, excessive alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure;
- Contraindicated in patients with renal impairment (e.g., serum creatinine ≥1.5 mg/dL for males, ≥1.4 mg/dL for females, or abnormal creatinine clearance);
- Potential for acute alteration of renal function when undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures requiring restricted intake of food and fluids;
- Decrease in Vitamin B12 levels;
- Hypersensitivity;
- Hypoglycemia, in elderly and debilitated patients when calorie intake is deficient, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On October 11, 2011 and June 26, 2013, DMEP provided written responses to the applicant's meeting request regarding the development of this XR FDC, where we agreed that bioequivalence studies comparing co-administration of the individual components to the 'to-be-marketed' XR FDC for each tablet strength, under fed and fasted conditions, would be appropriate to bridge the existing safety and efficacy data from studies of Tradjenta, Glumetza, and Jentadueto.

We also provided written responses to the Applicant's Type C/pre-NDA meeting request on January 6, 2015. We agreed that clinical summaries in Module 2.7 or integrated summaries (ISE/ISS) were not required as only Phase 1 studies were conducted for this NDA. As agreed, the applicant provided a Clinical Overview and narratives for all subjects who discontinued from the Phase 1 studies due to adverse events and who had serious adverse events. In addition, a 4-month safety update was submitted on November 16, 2015 as requested.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices (GCP)

All Phase 1 Clinical Pharmacology studies submitted in this application (1288.8, 1288.9, and 1288.11) were GCP compliant per the Applicant.

3.3 Financial Disclosures

All clinical investigators of the pivotal Phase 1 BE studies, 1288.11 and 1288.9, were full-time employees of the Applicant.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Office of Pharmaceutical Quality (OPQ) recommended approval of this NDA; see OPQ review dated April 18, 2016 for full details. A brief summary is provided here.

The combination product contains immediate release linagliptin and XR of metformin HCL by film coating linagliptin (b) (4) on readily available metformin XR tablet core. (b) (4) The nonclinical review verified that there are no new excipients or impurities in the proposed drug product.

Linagliptin drug coating solution contains arginine (b) (4). The metformin ER tablet core uses (b) (4)

4.2 Clinical Microbiology

No information related to clinical microbiology was included in this supplement.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was included in this supplement, and Dr. Carlson recommended approval. Please see his review in DARRTS dated May 3, 2016.

The nonclinical support for the safety of this FDC product is provided by cross-referencing information in the approved drug products, Tradjenta (NDA 201280), Jentadueto (NDA 201281), and Glumetza (NDA 21-748). There are no existing or new pharmacology/toxicology concerns for the drug substances proposed in this FDC product.

4.4 Clinical Pharmacology

The applicant aimed to establish the BE between the linagliptin/metformin XR FDC and the co-administration of individual components in order to bridge the existing safety and efficacy data from linagliptin (Tradjenta), metformin (Glumetza), and linagliptin/metformin IR FDC (Jentadueto). In order to achieve this, the applicant conducted two pivotal BE studies for two proposed strengths of Jentadueto XR:

- Study 1288.9 evaluated the BE of the linagliptin 5 mg/metformin XR 1000 mg FDC to co-administration of linagliptin 5 mg and 2 tablets of metformin XR 500 mg in fasted and fed conditions;
- Study 1288.11 evaluated the BE of 2 tablets of linagliptin 2.5/metformin XR 1000 mg FDC to co-administration of linagliptin 5 mg and 4 tablets of metformin XR 500 mg in fasted and fed conditions.

The Applicant's results from Study 1288.9, using 5/1000 mg FDC of linagliptin/metformin ER compared to that of a single-dose combination of individual components under fasted and fed conditions are summarized in Table 1.

Table 1: Study 1288.9 – Bioequivalence Evaluations for 5/1000 mg of Linagliptin/Metformin Dose

	Part 1 (fasted conditions)		Part 2 (fed conditions)	
	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV
Linagliptin				
AUC_{0-72}	100.4 (96.6, 104.3)%	11.8	94.7 (88.7, 101.1)%	9.2
C_{max}	108.1 (99.0, 118.0)%	27.1	98.2 (94.1, 102.6)%	6.1
Metformin				
AUC_{0-tz}	100.0 (93.0, 107.5)%	22.2	97.0 (92.2, 101.9)%	7.1
C_{max}	99.8 (92.5, 107.6)%	23.4	99.0 (95.0, 103.2)%	5.9

gCV: geometric coefficient of variation within subjects

Source: Clinical Overview, Table 2.1.1:2

The results from Study 1288.11, using 2 tablets of 2.5/1000 mg FDC of linagliptin/metformin ER compared to that of a single-dose combination of individual components under fasted and fed conditions are summarized in Table 2.

Table 2: Study 1288.11 – Bioequivalence Evaluations for 5/2000 mg of Linagliptin/Metformin Dose

	Part 1 (fasted conditions)		Part 2 (fed conditions)	
	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV	Adjusted gMean ratio of FDC/free combination (90% CI)	gCV
Linagliptin				
AUC_{0-72}	103.7 (100.7, 106.7)%	9.1	101.6 (93.7, 110.2)%	12.7
C_{max}	114.6 (107.7, 121.9)%	19.6	98.3 (86.5, 111.6)%	20.1
Metformin				
AUC_{0-tz}	96.5 (91.2, 102.0)%	17.6	97.8 (90.5, 105.6)%	11.7
C_{max}	98.0 (92.0, 104.3)%	19.9	105.9 (96.7, 115.9)%	13.8

gCV: geometric coefficient of variation within subjects
Source: Clinical Overview, Table 2.1.2:2

The results of these pivotal BE pharmacology studies demonstrated that the linagliptin/metformin XR FDC was bioequivalent to co-administration of individual components within the range of 80-125% for all tested tablet strengths. Dr. Chung found these results acceptable and recommended approval; please see his review dated April 27, 2016 for complete details and discussions of results.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Clinical studies supporting the new FDC product were Phase 1 BE studies in healthy volunteers. See section 4.4 for brief discussion of these studies. The applicant also conducted Study 1288.8, which was an open-label, randomized, single-dose, two-way crossover study evaluating the relative bioavailability of FDC to the free combination of linagliptin and metformin XR in healthy subjects.

5.2 Review Strategy

The Applicant cross-referenced the safety and efficacy data from NDAs previously reviewed for approval of Jentadueto, Glumetza, and Tradjenta in support of this NDA. Thus, the new clinical study data in the application were the two pivotal Phase 1 BE studies and Study 1288.8 as described previously. Therefore, I reviewed the safety data from the new Phase 1 BE studies and updated postmarketing safety data submitted with the application along with the 4-Month Safety Update for the safety review.

5.3 Discussion of Individual Studies/Clinical Trials

See section 4.4 for brief discussion of Phase 1 BE studies in healthy volunteers.

6 Review of Efficacy

Efficacy Summary

No clinical study evaluating the efficacy of linagliptin/metformin XR FDC was conducted. The efficacy for individual components was established under Tradjenta (NDA 201-280) and Glumetza (NDA 021-748). The clinical efficacy for combination therapy of linagliptin with metformin IR has been established under Jentadueto (NDA 201-281), and metformin IR and XR have been previously shown to have similar efficacy.

Therefore, the clinical development program for this FDC was to bridge the existing clinical efficacy and safety data by demonstrating the bioequivalence of the FDC tablets to the co-administration of individual components in health volunteers in pivotal Phase 1 BE studies. The results of these studies are summarized in section 4.4 above and more details can be found in Dr. Chung's review.

6.1 Indication

The proposed indication is an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4) treatment with both linagliptin and metformin (b) (4) is appropriate.

7 Review of Safety

Safety Summary

The review of safety of linagliptin used in combination with metformin IR during Jentadueto NDA did not identify any new additional safety concerns related to concomitant use and I expect that linagliptin used in combination with metformin XR would be similar. In addition, the review of safety data from Phase 1 studies and review of updated postmarketing data did not identify any new safety concerns.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In addition to BE studies 1288.9 and 1288.11 discussed in section 4.4, the applicant also conducted Studies 1288.8, which was an open-label, randomized, single-dose, two-way crossover study evaluating the relative bioavailability of FDC to the free combination of linagliptin and metformin XR in healthy subjects.

7.2 Adequacy of Safety Assessments

Safety assessments were adequate for the proposed NDA; as described above new safety data were not required for approval. Safety data from Phase 1 clinical studies in healthy volunteers are reviewed for completeness.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred.

7.3.2 Nonfatal Serious Adverse Events

Three subjects reported serious adverse events (SAEs) which also led to study discontinuation. All SAEs in these three subjects were accidental injuries and do not appear to be causally related to the study drug as Studies 1288.8 and 1288.9 were single-dose studies and the reported events were not temporally related to study drug.

The narratives of 3 SAEs are briefly summarized here:

- Subject #209 (Study 1288.8): A 23-year old man reported a motorcycle accident a month after receiving the study drug (combination of 5 mg linagliptin and 1000 mg metformin XR in fed state) during the washout period. He discontinued study participation due to the accident.
- Subject #207 (Study 1288.9): A 50-year old man received a single dose of study drug (combination of 5 mg linagliptin and 1000 mg metformin XR in fed state) and 26 days later experienced a severe fall during an inline skating leading to severe fracture of pelvis and left acetabulum of the hip.
- Subject #211 (Study 1288.9): An 18-year old female received a single dose of study drug (combination of 5 mg linagliptin and 1000 mg metformin XR in fed state) and 15 days later had a severe traffic accident and experienced multiple injuries related to the accident leading to hospitalization.

7.3.3 Dropouts and/or Discontinuations

Three additional subjects reported adverse events leading to study discontinuation. Review of these cases did not lead to any new safety concerns. The narratives of 3 subjects who discontinued are briefly summarized here:

- Subject #215 (Study 1288.9; received FDC in fed state): A 42-year old woman received a single dose of study drug and reported a mild non-serious loss of appetite that resolved the next day. The next day, she developed a mild exanthema on the upper body which was considered non-serious. No treatment was given for rash and it resolved in 2 days. Due to the single dose design of study period, study drug was neither reduced nor discontinued due to exanthema and appetite loss. The healthy volunteer was discontinued from the study due to exanthema on the upper body on June 23, 2013. [***Reviewer's comment: The exanthema is consistent with hypersensitivity reaction which is already labeled event.]***
- Subject #120 (Study 1288.8; received 5/1000 mg FDC in fasted state): A 30-year old woman experienced influenza-like illness during washout after she received the study drug. She did not receive the second treatment.
- Subject #204 (Study 1288.8; received 5/1000 mg FDC in fed state): A 21-year old man was removed from the study due to elevated total and direct bilirubin at Day 3 where total bilirubin was 3.24 mg/dL (range 0.19 to 1.69 mg/dL) and direct bilirubin of 0.48 mg/dL (range 0 to 0.35 mg/dL); repeat values were 2.74 mg/dL and 0.41 mg/dL respectively the next day. The Investigator decided to discontinue the subject.

8 Postmarket Experience

The cumulative post-marketing exposure since its approval is estimated to be 581,162 patient-years worldwide as of April 2015.

The applicant submitted a 12-month Periodic Benefit Risk Evaluation Report for Jentadueto during reporting period of May 3, 2014 to May 2, 2015 that summarized safety information related to concomitant administration of linagliptin and metformin HCl immediate release formulation. During this period (on May 22, 2014), the labeling was updated with 'hypersensitivity reactions' in Warnings and Precautions and other relevant sections of labeling. In addition, a new DAARTS Tracked Safety Issue was created for all DPP-4 inhibitors regarding arthralgia on March 25, 2015 and a safety update label change notification was sent on April 24, 2015. In August 2015 the labeling for all DPP-4 inhibitors including linagliptin was updated with a new Warnings and Precaution section about the join pain that can be severe and disabling based on postmarketing and literature data.

In addition, as a 4-Month Safety Update (4MSU), the applicant provided updated safety data collected from May 3, 3015 up to July 27, 2015. During this reporting interval, the overall patient exposure to marketed Jentadueto was estimated to be 102,946 patient-years (b) (4) There were no ongoing clinical trials with combination of linagliptin and metformin HCl immediate- or extended-release formulation during this reporting period.

Review of these safety data showed that the postmarketing adverse events were consistent with the current safety issues described in the Prescribing Information for Tradjenta and Jentadueto.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

Labeling negotiations are ongoing at the time of this review.

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/s/

HYON J KWON
05/18/2016

LISA B YANOFF
05/18/2016