CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208026Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	23 May 2016
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208026
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	27 Jul 2015
PDUFA Goal Date	27 May 2016
Proprietary Name / Established (USAN) names	Jentadueto XR/ Linagliptin and metformin hydrochloride extended-release
Dosage forms / Strength	Oral tablets with the following dosage strengths: 5 mg linagliptin/1000 mg metformin hydrochloride extended-release 2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release
Proposed 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
Recommended:	Approval

Cross Discipline Team Leader Review

1. Introduction

Boehringer Ingelheim Pharmaceuticals, Inc. is submitting a New Drug Application (NDA) #208026 under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the fixed-combination drug product linagliptin /metformin hydrochloride extended-release for the treatment of patients with type 2 diabetes mellitus (T2DM).

The regulatory pathway through section 505(b)(1) is appropriate because the Applicant is the sponsor of the linagliptin product (Tradjenta, NDA 201280) and provides a Letter of Authorization from the sponsor of the metformin extended-release product (Glumetza, NDA 021748).

The proposed indication is 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.

2. Background and Application Overview

The NDA is for linagliptin/metformin extended release, a fixed combination drug [also known as a fixed-dose combination (FDC)] of linagliptin, a dipeptidyl peptidase 4 inhibitor (DPP4-i) and metformin, the only member of the biguanide class. Both components are approved in the U.S. as individual products, and an immediate release formulation of the combination is also approved in the U.S. and marketed as Jentadueto. The proposed trade name Jentadueto XR has been determined to be acceptable by the Division of Metabolism and Endocrinology Products and by the Division of Medication Error and Prevention Analysis and will be used interchangeably with the nonproprietary name throughout this memo.

Linagliptin is the third DPP4-i approved in the U.S. Linagliptin improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by inhibiting the inactivation of GLP-1 and GIP (incretin hormones) and prolonging the incretin effect on beta cells (serum glucose-dependent insulin stimulation) and alpha cells (glucagon suppression). GLP-1 in particular has other effects that contribute to improved glucose control in diabetics, such as appetite suppression and slowing of the rate of gastric emptying. Linagliptin is dosed at 5 mg once daily.

Metformin is effective in decreasing hepatic glucose output and decreasing peripheral glucose utilization. Metformin gained a first-line treatment recommendation by the American Diabetes Association and other diabetes professional organizations, and is widely used in the treatment of T2DM. The Prescribing Information for Glumetza (metformin XR) states that '*in general, clinically significant responses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms. The starting dose of GLUMETZA is 1000 mg once daily which in order to maximize therapeutic efficacy must be taken with food preferably in the evening. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2000*

mg once daily with the evening meal. If glycemic control is not achieved on GLUMETZA 2000 mg once daily, a trial of GLUMETZA 1000 mg twice daily should be considered.'

The proposed strengths for Jentadueto XR are 5 mg linagliptin/1000 mg metformin hydrochloride extended-release 2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release. The proposed dosing regimen is as follows:

- in patients currently not treated with metformin, initiate treatment with 5 mg linagliptin/1000 g metformin hydrochloride extended-release once daily (b) (4)
- In patients already treated with metformin, the (b) (4) total daily starting dose of JENTADUETO XR is 5 mg linagliptin and a similar total daily dose of metformin
- In patients already treated with TRADJENTA and metformin or JENTADUETO switch to JENTADUETO XR containing 5 mg of linagliptin total daily dose and a similar total daily dose of metformin

In addition to adequate clinical trial data, approval of an FDC for the treatment of T2DM is dependent on demonstration of bioequivalence (BE) of the FDC and the two individual components administered together. With demonstration of BE, the precedent within the Division of Metabolism and Endocrinology Products for products containing metformin combined with another oral antidiabetic agent is to then approve the FDC for either a 'narrow' indication (e.g. patients *who are not adequately controlled on a regimen containing metformin or linagliptin, or in patients who are already treated with both linagliptin and metformin*) or a 'broad' indication (e.g. *when treatment with both linagliptin and metformin is appropriate*). The narrow indication is typically granted based on clinical trial data showing additional placebo-adjusted glycemic lowering from the second drug (e.g. linagliptin) to metformin. To allow treatment with the FDC in patients who are treatment naïve, the applicant must show that the coadministration (or alternatively, the FDC) is more effective than each component alone, in patients not treated with either drug prior to the trial, i.e. show contribution of claimed effect of each component as per 21CFR 300.50. The typical approach is to conduct a factorial study with each of the single agents being compared to the combination; such a study was submitted with the original Jentadueto NDA and was used to support the initial approval of Jentadueto with the broader indication.

The basis for the request for approval of the proposed (broad) indication for Jentadueto XR is the following:

- Results of the pivotal bioequivalence (BE) studies
- Clinical comparability between metformin twice daily (Glucophage) and once daily (Glumetza) shown in the original NDA for Glumetza
- The efficacy and safety of co-administration of linagliptin and metformin twice daily (Glucophage) as add-on to metformin in the original Tradjenta NDA and as initial therapy in the factorial study 1218.46 submitted to support the approval of Jentadueto for the 'broad' indication

This summary memo contains a high-level overview of the important review findings of the NDA. Please see the individual reviews for each discipline for detailed discussions. This memo references the following documents.

Subject	Author	Date in DARRTS
Clinical Pharmacology (OCP) review	Dr. Sang Chung and Dr. Manoj Khurana	27 Apr 2016
Chemistry Manufacturing and Controls (Quality) review	Team review, Technical Lead Dr. Suong Tran	18 Apr 2016 (in Panorama)
Clinical Efficacy and Safety Review	Dr. Hyon Kwon	18 May 2016
Nonclinical review (Pharmacology/toxicology)	Dr. David Carlson	20 Apr 2016
Division of Pediatric and Maternal Health consult	Dr. Miriam Dinatale	28 Apr 2016
Office of Study Integrity and Surveillance inspection reviews	Dr. Li-Hong Paul Yeh	19 Feb 2016, 11 Mar 2016, 15 Mar 2016
Division of Medication Error Prevention and Analysis consult review	Dr. Sarah Vee and Dr. Yelena Maslov	29 Apr 2016
Division of Medical Policy Programs (DMPP) consult review	Team review	5 May 2016

3. CMC

The recommendation from the Office of Pharmaceutical Quality (including the Overall Manufacturing Inspection Recommendation) is approval. NDA 201280 Tradjenta (linagliptin), by the same applicant, is referenced for all CMC information on the drug substance linagliptin. The NDA is currently approved and the reference is adequate. NDA 201281 Jentadueto (linagliptin/metformin HCl), by the same applicant, is referenced for all CMC information on the drug substance metformin HCl. The NDA is currently approved and the reference is adequate.

The drug product is a film-coated tablet consisting of immediate release linagliptin and extended release metformin HCl, with two strengths: 5 mg/1000 mg and 2.5 mg/1000 mg linagliptin (immediate release)/metformin hydrochloride (extended release). Please see the Quality review for details.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer Dr. David Carlson recommends approval of this NDA. No new nonclinical information was submitted to support the proposed linagliptin and metformin XR FDC tablets. Nonclinical support for the safety of the proposed FDC tablets is claimed from cross referencing information in approved drug products. As noted above the drug substances in the proposed FDC tablets are identical to those previously approved. Nonclinical review of the drug product excipients and specifications independently verified that there are no new excipients or impurities in the proposed drug product. Please see Dr. Carlson's review for details.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer Dr. Sang Chung recommends approval of this NDA. The applicant conducted two pivotal BE studies because there are two proposed strengths for Jentadueto XR under fasted or fed conditions. According to Dr. Chung, BE was demonstrated for both strengths of Jentadueto XR referencing corresponding co-administration of Tradjenta and Glumetza under both fasted and fed conditions.

The data from these two studies are shown below.

Study 1288.9 (dose level investigated: 5/1000 mg)

	Part 1 (fasted conditions)	Part 2 (fed conditions)
Linagliptin		
AUC_{0-72}	100.4 (96.6, 104.3)%	94.7 (88.7, 101.1)%
C_{max}	108.1 (99.0, 118.0)%	98.2 (94.1, 102.6)%
Metformin		
AUC_{0-72}	100.0 (93.0, 107.5)%	97.0 (92.2, 101.9)%
C_{max}	99.8 (92.5, 107.6)%	99.0 (95.0, 103.2)%

Study 1288.11 (dose level investigated: 5/2000 mg)

	Part 1 (fasted conditions)	Part 2 (fed conditions)
Linagliptin		
AUC_{0-72}	103.7 (100.7, 106.7)%	101.6 (93.7, 110.2)%
C_{max}	114.6 (107.7, 121.9)%	98.3 (86.5, 111.6)%
Metformin		
AUC_{0-72}	96.5 (91.2, 102.0)%	97.8 (90.5, 105.6)%
C_{max}	98.0 (92.0, 104.3)%	105.9 (96.7, 115.9)%

Source: Clinical Pharmacology review

Dr. Chung noted no concerns with the study methodology. Site inspections were also acceptable (see section 11 of this memo). I agree with Dr. Chung that the pivotal BE study results support approval of this NDA.

6. Clinical Microbiology

Please see the Quality review

7. Clinical/Statistical- Efficacy

The basis for establishment of efficacy for Jentadueto XR is the previous review and approval of Jentadueto. No clinical efficacy i.e. Phase 3 studies were submitted with this NDA.

8. Safety

The basis for the safety evaluation of Jentadueto XR is the previous review and approval of Jentadueto. Dr. Kwon's safety review included review of narratives for all subjects who discontinued from the Phase 1 studies due to adverse events and who had serious adverse

events, the 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. Please see her review for details.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this sNDA.

10. Pediatrics

Because this product is a new formulation of the combination of linagliptin and metformin from that approved previously, the product approval does trigger requirements under the Pediatric Research Equity Act (PREA). In keeping with usual practice, the PREA requirements for the linagliptin monotherapy product (1766-1 and 1766-2) will apply to the NDA for the combination product.

Of note, the Division is considering a release and reissue of the monotherapy PREA PMR 1766-2 in order to update the PMR description to reflect current agreements regarding protocol design (i.e., linagliptin and another antidiabetic product from this sponsor [empagliflozin] both on a background of metformin will be compared against a single placebo arm). This trial design was agreed upon by the Division and by the Pediatric Review Committee (PeRC) and is reflected in the iPSP for NDA 208026.

11. Other Relevant Regulatory Issues

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the bioanalytical portion of studies 1288-9 and 1288-11 (b) (4). This was determined to be acceptable. See review in DARRTS dated 15 Mar 2016.

OSIS also conducted an inspection of the bioanalytical portion of studies 1288-9 and 1288-11 (b) (4). The final classification for (b) (4) is voluntary action indicated (VAI). OSIS concluded that data from this study are acceptable for review. See review in DARRTS dated 19 Feb 2016.

OSIS also conducted clinical inspection at Boehringer Ingelheim Pharma GmbH & Co, KG, Biberach/Riss, where clinical portions of the BE studies were carried out. This inspection also found no issues and reported the pivotal BE data are acceptable for review. See review in DARRTS dated 11 Mar 2016.

12. Labeling

Labeling for Jentadueto XR for the most part should follow labeling of the Jentadueto product. Two unique issues are as follows:

Compliance with the Pregnancy and Lactation Labeling Rule (PLLR):
The proposed label for Jentadueto XR differs from the Jentadueto product in that it proposes new language to conform to the PLLR format. A consult from the Division of Pediatric and Maternal Health was requested by the Division for input on the labeling. Please see Dr. Miriam Dinatale's review in DARRTS. Development of the PLLR language was an evolving process and the approved label will contain the final agreed upon language.

A line-by-line labeling reviewed will be conducted separately.

The Division of Medication Error Prevention and Analysis reviewed the carton and container labeling and determined it to be acceptable. See review in DARRTS.

The Division of Medical Policy Programs (DMPP) reviewed the Medication Guide.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The clinical efficacy and safety of the individual components in the proposed fixed combination of linagliptin and metformin XR have been established in the Tradjenta and Glumetza NDAs, respectively. The efficacy and safety of linagliptin given once daily as add-

on to metformin given twice daily was demonstrated using adequate and well-controlled Phase 3 studies in the original NDA for Tradjenta (linagliptin). The efficacy and safety of once daily metformin XR was comparable to metformin IR twice daily in the Glumetza NDA. In addition, the contribution to glycemic lowering of each of the individual components was demonstrated in an adequate and well-controlled factorial study in treatment naïve patients and submitted to support approval of Jentadueto for the 'broad' indication.

Therefore, the data submitted to support the proposed linagliptin/metformin XR product were from relative bioavailability studies designed to bridge the existing clinical efficacy and safety data by demonstrating bioequivalence (BE) of each fixed-combination tablet to the co-administered free combinations of the individual components.

The pivotal BE studies 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. Hence, the overall data submitted with this NDA support approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

- Recommended Comments to Applicant

Labeling comments will be communicated to the applicant separately.

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/s/

LISA B YANOFF
05/26/2016

JEAN-MARC P GUETTIER
05/27/2016

I concur. Dr. Yanoff's review serves as the Divisional Summary memo for this application. Efficacy and safety of linagliptin and metformin co-administration was established with data from new drug applications 201280 and 201281. The product in this application combines linagliptin with the extended release version of metformin and has met the requirements under 21 CFR 300.50. There are no issues that preclude approval.