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).

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