CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum

Pharmacology/Toxicology
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Products

Date	13 October 2014
NDA #	206073
Sponsor	Boehringer Ingelheim
Drug	Empagliflozin/linagliptin FDC tablet
Primary Reviewer	David B. Carlson, PhD
Secondary Reviewer	Patricia Brundage, PhD

Boehringer Ingelheim is seeking approval for the fixed-dose combination product of linagliptin and empagliflozin as a treatment for type 2 diabetes. Both pharmaceutical components are currently approved for the chronic treatment of type 2. Linagliptin is a dipeptidylpeptidase-4 (DPP4) inhibitor approved in 2011 (NDA 201280) and empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor (NDA 204629) approved during the review cycle. The mechanisms of action of the two different drug classes are distinct but complementary on glucose control. Boehringer Ingelheim is the primary NDA holder for both linagliptin and empagliflozin.

Dr. David Carlson, the primary nonclinical reviewer, recommends approval of NDA 206073. *I concur with Dr. Carlson's recommendation.* The recommendation is based on the information for linagliptin and empagliflozin as monotherapies, and on the toxicology studies conducted with the drugs in combination to assess general toxicity and embryofetal development.

The toxicology of linagliptin and empagliflozin in combination was evaluated in a 3-month study in rats. Each drug was evaluated separately and in combination for comparison. No additive or unique toxicity was observed with the drugs in combination. Toxicity associated with the co-administration of the two drugs at exposures ≥14-times the clinical exposure was attributable to the SGLT2 inhibitor empagliflozin and is consistent with the established toxicology profile of empagliflozin.

Co-administration of the drugs in rats caused an increase in empagliflozin exposure (2- to 3-fold), which was associated with an increase in renal and hepatic toxicity at the highest dose combination (>50X clinical exposure) compared to that of empagliflozin alone. There was also a less consistent decrease in linagliptin exposure (up to 3-fold) with co-administration of the drugs. Similar changes in the pharmacokinetic profiles of the two drugs when co-administered were not observed in humans in the bioequivalence and pharmacokinetic trials with the linagliptin/empagliflozin FDC. Clinical drug-drug interactions between empagliflozin and linagliptin at clinical doses is unlikely based on in vitro metabolic enzyme induction and inhibition assays with the individual drugs, and on co-incubation assays of the two drugs in human hepatocytes. Although there is presently no mechanistic explanation for the systemic drug exposure changes in the rats, the clinical relevance is considered negligible.

An embyrofetal development study in rats was conducted by the applicant. The administration of linagliptin and empagliflozin alone and in combination was not teratogenic, which is concordant with the previous findings with the individual drugs in rats and rabbits.

As both drugs target the kidney, the embyrofetal development study included histopathological examination of fetal kidneys. Linagliptin accumulates in kidney tubules due to high DPP4 expression and DPP4-specific binding. Empagliflozin, which targets SGLT2 in the renal proximal tubules, causes changes in renal histology with chronic exposure and may affect fetal renal development and maturation, as determined from prior juvenile rat toxicology studies in this drug class. There was no evidence of kidney toxicity with linagliptin and empagliflozin administered alone or in combination at very high multiples of clinical exposure in the embyrofetal development study, suggesting a low likelihood of an overt toxicological interaction between the two drugs on renal development.

The combination linagliptin and empagliflozin toxicity studies in rats did not identify any potential interactions between the drugs to suggest an elevated clinical risk with FDC treatment. Labeling for the combination product will be consistent with the labeling for the individual monotherapies of linagliptin and empagliflozin.

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/s/

PATRICIA M BRUNDAGE
10/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206-073
Supporting document/s:	SDN-1
Applicant's letter date (CDER Stamp Date):	30 January, 2014
Product:	Empagliflozin / linagliptin FDC tablets
Indication:	Type 2 Diabetes Mellitus treatment
Applicant:	Boehringer Ingelheim Pharmaceuticals (BI)
Review Division:	Metabolism and Endocrinology Products
Reviewer:	David B. Carlson, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
Division Director / Deputy Director:	Jean-Marc Guettier, M.D. Eric Colman, M.D.
Project Manager:	Raymond Chiang, M.S.
Review Completion Date:	05 October, 2014

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