CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212614Orig1s000

SUMMARY REVIEW

Division Summary Memo for Regulatory Action and CDTL review

Date	January 24, 2020
From	Patrick Archdeacon, MD Acting Associate Director for Therapeutics Division of Metabolism and Endocrinology Products
NDA # / Sequence #:	NDA 212614
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission Receipt	March 27, 2019
PDUFA Goal Date	January 27, 2020
Proprietary Name / Established (USAN) names	Empagliflozin + Linagliptin + Metformin hydrochloride (HCl) Extended-Release
(Proposed) Trade name	Trijardy XR
Dosage forms / Strength	The Applicant is seeking approval of film-coated tablets containing the following empagliflozin/linagliptin/metformin extended-release dosage strengths: 5mg/2.5mg/1000mg, 10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg, and 25mg/5mg/1000mg
Recommended Action	Approval
New Recommended Indication(s)/Populations(s)	1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus 2. To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease

1. Introduction

This document serves as the 'Summary Basis for Regulatory Action' memo for the original new drug application (NDA) for a fixed combination drug product (FCDP) comprising empagliflozin, linagliptin, and metformin extended-release. Each of these components of the proposed FCDP is indicated to improve glycemic control in patients with type 2 diabetes mellitus (T2D). In addition, empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

This memo references the following documents/sources:

Subject	Author	Date
Quality Assessment	Joseph Leginus (Drug Substance), Elise Luong (Drug Product and Environmental Analysis), Christina Capacci-Daniel (Process/Microbiology/Facility), Hangsong Chen (Biopharmaceutics), Muthu Ramaswamy (Application Technical Lead)	December 9, 2019
Pharmacology/Toxicology	David Carlson	December 9, 2019
Clinical Pharmacology	S.W. Johnny Lau	December 6, 2019
Statistics	Yi Ren	December 19, 2019
Clinical	Frank Pucino	January 21, 2020
Division of Medication Error Prevention and Analysis (DMEPA)	Ariane Conrad	November 26, 2019
Patient Labeling Review	Lonice Carter (Patient Labeling Reviewer), Meena Savani (Regulatory Reviewer)	December 30, 2019
Labeling Consult Review	Meena Savani	December 23, 2019
Clinical Inspections	Cynthia Kleppinger	December 4, 2019

2. Background

Type 2 diabetes (T2D) is a disease of abnormal glucose homeostasis which results in hyperglycemia. Glycemic control has been the accepted target for therapies as studies have shown that improved glycemic control can improve clinical outcomes.

Empagliflozin is an SGLT2 inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2D. It inhibits glucose reabsorption in the proximal

tubules of the kidney, thereby increasing urinary excretion of glucose and reducing plasma glucose levels.

Linagliptin is a DPP-4 inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2D. By inhibiting the degradation of incretin hormones, linagliptin lower plasma glucose levels.

Metformin is a biguanide approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2D. It lowers plasma glucose level through decreasing hepatic gluconeogenesis and improving peripheral insulin sensitivity.

New data submitted support from this NDA consists of CMC data (including dissolution studies supporting a biowaiver), BA/BE studies, and two new supportive clinical trials. The NDA also relies on previously submitted data owned by the applicant that has been reviewed in the context of other formulations of drug products that include one or more of the components of Trijardy XR (i.e., empagliflozin, linagliptin, and metformin).

3. CMC

The recommendation from the Office of Pharmaceutical Quality (OPQ) is that the CMC information is adequate to support the approval of NDA 212614. Dr. Joseph Leginus reviewed the Drug Substance information for metformin hydrochloride, empagliflozin, and linagliptin; Dr. Elise Luong reviewed the Drug Product information (including drug product composition, excipient compatibility, batch analysis, container closure system, and stability information) and the environmental anaylsis, Dr. Christine Cappaci-Daniel reviewed the drug process and microbiology data (including a risk assessment for the manufacturing process control), Dr. Hangsong Chen reviewed the biopharmaceutical data (including the dissolution method, supporting dissolution data, dissolution acceptance criteria, alcohol induced dose dumping data, and the biowaiver request). Dr. Muthu Ramaswamy performed a risk assessment for the finished product critical quality attributes. Together, the OPQ review team concluded that there are no outstanding deficiencies related to drug substance, drug product, process, facilities, biopharmaceutics, environmental anaylsis, or container and carton label. Please see the integrated OPQ review for additional details. I concur with their conclusions.

Trijardy XR (empagliflozin/linagliptin/metformin HCl) extended release tables are manufactured as film-coated oval shaped tablets in 4 different strengths:

- 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release
- 10 mg empagliflozin/5 mg linagliptin/1000 mg metformin hydrochloride extended-release
- 12.5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release
- 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin hydrochloride extended-release

The Trijardy XR tablet manufacturing process uses [redacted] a metformin extended release (ER) core. The ER table core is [redacted] tablets are printed with their strength and packaged.

The acceptability of the final product formulation was established based on data available from bioequivalence (BE) studies and from available dissolution data. Dissolution acceptance criteria of Q= [redacted]% in 45 minutes and Q= [redacted]% in 30 minutes were set. For metformin HCl, an acceptance criterion of NLT [redacted]% release in 12 hours was accepted. The BE studies used the highest (25 mg/5 mg/1000 mg) and the lowest (5 mg/ 5 mg/1000 mg) strength empagliflozin/linagliptin/metformin HCl extended release tablets. The applicant requested a biowaiver for the two intermediate strengths. Dr. Chen concluded that the dissolution profiles of the intermediate strengths were similar to the dissolution profiles of the highest and lowest strength tablets. For that reason, the biowaiver for the intermediate strength tablets was deemed acceptable.

4. Nonclinical Pharmacology/Toxicology

Dr. David Carlson from the Division of Metabolism and Endocrinology Products (DMEP) reviewed the nonclinical data supporting NDA 212614 and recommends approval. Please see Dr. Carlson's review for additional details. I concur with his conclusions.

The drug substances in the proposed empagliflozin/linagliptin/metformin extended release tablets have been the subject of extensive previous nonclinical studies: each active ingredient is approved as monotherapy and each are used in other FDCP tablets. The primary objective of the nonclinical development program of Trijardy XR was to rule out potentially adverse interactions from coadministration.

A 13-week rat empagliflozin/linagliptin/metformin combination toxicity study was conducted to address the potential of adverse interactions and also to bridge to previous pharmacology/toxicology assessments of the individual drug substances. The doses selected for the toxicity study results in exposures that approximate 1x, 5x, and 10x clinical exposures at the maximum recommended human dose (MRHD). Dr. Carlson concluded that the study showed no evidence of supra-additive of synergistic toxicities.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Johnny Lau from the Office of Clinical Pharmacology reviewed the clinical pharmacology data supporting NDA 212614. He concluded that the data support approval. Please see Dr. Lau's review for additional details. I concur with his conclusions.

The applicant conducted three BA/BE studies to support NDA 212614 (see Table 1). Studies 1361.3 and 1361.11 are the pivotal BE studies. Because metformin should be taken with food to improve tolerability, these studies were done in the fed state.

Table 1: BA/BE studies supporting NDA 212614

BI study no. Report no.	Objective and description	Study part, meal status	FDC tablet strength tested [mg]	Free combination dose tested [mg]
1361.1 [c12820904]	Relative bioavailability, single-dose, pilot study	1, fed	E25/L5/M1000	E25 + L5 + 2x M500
		2, fasted	E25/L5/M1000	E25 + L5 + 2x M500
		3, fed	E10/L5/M1000	E10 + L5 + 2x M500
1361.3 [c20062581]	Bioequivalence, single-dose, pivotal study	1, fed	E25/L5/M1000	E25 + L5 + 2x M500
1361.11 [c26461305]	Bioequivalence, single-dose, pivotal study	1, fed	E5/L2.5/M1000	E10 + L5 + 4x M500

E: empagliflozin; L: linagliptin; M: metformin extended release
Source: FDA Clinical Pharmacology Review

Study 1361.3 was a single-dose, randomized, 2-way crossover study in 30 healthy male and female participants under fed condition to assess the BE of a 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin XR tablet to a 25 mg empagliflozin tablet, a 5 mg linagliptin tablet, and two 500 mg metformin XR tablets. Study 1361.11 was a single-dose, randomized, 2-way crossover study in 30 healthy male and female participants under fed condition to assess the BE of two 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR tablets to a 10 mg empagliflozin tablet, a 5 mg linagliptin tablet, and four 500 mg metformin XR tablets. Dr. Lau concluded that the results of Study 1361.3 and Study 1361.11 supported a finding of BE for the highest strength Trijardy XR tablets and relevant individual API drug products and for the lowest strength Trijardy XR tablets and relevant individual API drug products. Dr. Lau noted that the sponsor had requested and received a biowaiver for the intermediate strength Trijardy XR tablets (see Dr. Chen's Biopharmaceutics review in the integrated review from the Office of Pharmaceutical Quality). Dr. Lau also noted that Office of Study Integrity and Surveillance conducted inspections for Studies 1361.3 and 1361.11 and found the data acceptable for review. In addition, Dr. Lau reviewed the bioanalytical method validations for empagliflozin, linagliptin, and metformin used in the studies and found them acceptable.

6. Clinical/Statistical- Efficacy

Dr. Yi Ren from the Office of Biostatistics and Dr. Frank Pucino from the Division of Metabolism and Endocrinology Products evaluated the data supporting the efficacy for NDA 212614. Both Dr. Ren and Dr. Pucino concluded that the data support approval. I concur with their conclusions.

The pivotal study supporting the efficacy of Trijardy XR is Study 1275.1, a factorial design study that compared empagliflozin and linagliptin FDCP to the individual component drug products in both treatment naïve and metformin treated patients with T2D.
This study was previously reviewed under NDA 206073 for the approval of Glyxambi (an empagliflozin and linagliptin FDCP approved in January 2015). The submission to NDA 212614 also included clinical data from two supportive studies: Study 1275.9 and Study 1275.10, both of which were non-responder add-on studies whose results were not available during the original review of the Glyxambi NDA. Study 1275.9 evaluated empagliflozin as an

add-on treatment to a regimen of metformin and linagliptin; Study 1275.10 evaluated linagliptin as an add-on treatment to a regiment of metformin and empagliflozin (see Table 2).

Table 2: Study Designs of 1275.9 and 1275.10

Study	Design	Treatment	Treated Set (N)
1275.9	24-week add-on study of Empa	Add-on to Met + Lina 5: • Empa 25 • Empa 10 • Placebo	332
1275.10	24-week add-on study of Lina	Add-on to Met + Empa 25: • Lina 5 • Placebo	224
		Add-on to Met + Empa 10: • Lina 5 • Placebo	254

Empa: empagliflozin; Lina: linagliptin; Met: metformin

Source: FDA Statistics Review

Dr. Ren conducted repeated washout analyses of the primary and key secondary endpoints for Studies 1275.9 and 1275.10; the results were similar to the applicant's MMRM analysis results (see Table 3 and Table 4). Please see Dr. Ren's statistical review for additional details. Both FDA reviewers concluded that Study 1275.9 showed superior improvement in HbA1c for empagliflozin (25 mg or 10 mg) compared to placebo when added to metformin and linagliptin; both FDA reviewers concluded that Study 1275.10 showed superior improvement in HbA1c for linagliptin 5 mg compared to placebo when added to metformin and empagliflozin. Both FDA reviewers also concluded that the results of Study 1275.9 and Study 1275.10 were consistent with the results of the pivotal study (Study 1275.1) and did not provide new information important for labeling. For that reason, the Trijardy XR labeling will include results from the previously reviewed Study 1275.1 (and as already shown in the Glyxambi labeling) but will not include results from Studies 1275.9 and 1275.10.

Table 3: Analyses of Primary and Key Secondary Endpoints, Study 1275.9

Study 1275.9 [1]	Metformin+lina 5 mg		
	Empa 25 mg	Empa 10 mg	Placebo
Total patients analyzed, N	110	112	110
Mean baseline HbA_{1c} (SE)	7.97 (0.08)	8.00 (0.08)	7.99 (0.08)
Change from baseline			
Mean HbA_{1c} (SE)	-0.55 (0.09)	-0.61 (0.10)	0.06 (0.09)
Adjusted[2] mean HbA_{1c} (SE)	-0.56 (0.08)	-0.61 (0.08)	0.07 (0.08)
Comparison vs. placebo			
Adjusted[2] mean HbA_{1c} (SE)	-0.63 (0.11)	-0.69 (0.12)	
95% CI	(-0.86, -0.41)	(-0.91, -0.46)	
p-value	<0.0001	<0.0001	
Mean baseline FPG (SE)	169.9 (4.0)	168.0 (3.7)	163.2 (3.1)
Change from baseline			
Mean FPG (SE)	-31.7 (4.5)	-24.0 (4.1)	6.4 (4.6)
Adjusted[2] mean FPG (SE)	-29.9 (3.7)	-23.4 (3.6)	4.0 (3.6)
Comparison vs. placebo			
Adjusted[2] mean FPG (SE)	-33.9 (5.2)	-27.3 (5.1)	
95% CI	(-44.0, -23.7)	(-37.4, -17.3)	
p-value	<0.0001	<0.0001	
Mean baseline body weight (SE)	84.38 (1.83)	88.33 (1.95)	82.26 (1.87)
Change from baseline			
Mean body weight (SE)	-2.38 (0.25)	-2.78 (0.26)	-0.15 (0.25)
Adjusted[2] mean body weight (SE)	-2.40 (0.25)	-2.71 (0.25)	-0.21 (0.25)
Comparison vs. placebo			
Adjusted[2] mean body weight (SE)	-2.19 (0.35)	-2.50 (0.35)	
95% CI	(-2.87, -1.51)	(-3.20, -1.81)	
p-value	<0.0001	<0.0001	

SE: standard error
Empa: empagliflozin; Lina: linagliptin
[1] The results were based on the requested washout analyses where missing data in an endpoint from both arms were imputed using observed data from the placebo arm.
[2] ANCOVA model included baseline HbA1c as linear covariate and baseline eGFR, geographical region, and treatment as fixed effects.

Source: FDA Statistical Review

Table 4: Analyses of Primary and Key Secondary Endpoints, Study 1275.9

Study 1275.10 [1]	Metformin+empa 25 mg		Metformin+empa 10 mg	
	Lina 5 mg	Placebo	Lina 5 mg	Placebo
Total patients analyzed, N	112	112	126	128
Mean baseline HbA_{1c} (SE)	7.83 (0.07)	7.89 (0.08)	8.03 (0.08)	8.01 (0.08)
Change from baseline				
Mean HbA_{1c} (SE)	-0.55 (0.07)	-0.17 (0.07)	-0.56 (0.09)	-0.23 (0.07)
Adjusted[2] mean HbA_{1c} (SE)	-0.56 (0.07)	-0.15 (0.07)	-0.56 (0.07)	-0.23 (0.07)
Comparison vs. placebo				
Adjusted[2] mean HbA_{1c} (SE)	-0.40 (0.10)		-0.34 (0.10)	
95% CI	(-0.59, -0.22)		(-0.53, -0.15)	
p-value	<0.0001		0.0006	
Mean baseline FPG (SE)	152.9 (2.8)	156.1 (3.5)	160.6 (3.6)	156.6 (3.1)
Change from baseline				
Mean FPG (SE)	-10.2 (3.4)	-6.0 (3.3)	-9.8 (4.5)	3.1 (3.0)
Adjusted[2] mean FPG (SE)	-11.0 (2.8)	-5.2 (2.7)	-8.3 (3.2)	1.7 (3.1)
Comparison vs. placebo				
Adjusted[2] mean FPG (SE)	-5.8 (3.9)		-10.0 (4.5)	
95% CI	(-13.4, 1.9)		(-18.7, -1.2)	
p-value	0.1391		0.0254	

SE: standard error
Empa: empagliflozin; Lina: linagliptin
[1] The results were based on the requested washout analyses where missing data in an endpoint from both arms were imputed using observed data from the placebo arm.
[2] ANCOVA model included baseline HbA1c as linear covariate and baseline eGFR, geographical region, and treatment as fixed effects.

Source: FDA Statistical Review

7. Safety

Dr. Frank Pucino of the Division of Metabolism and Endocrinology Products also reviewed the clinical safety data submitted to NDA 212614. Dr. Pucino reviewed the data from studies 1275.1, 1275.9, and 1275.10 and concluded that they support a positive benefit-risk

assessment for Trijardy XR; please see his clinical review for additional details. Dr. Pucino recommended approval of NDA 212614. I concur with his recommendation.

The safety database for NDA 212614 provides additional data beyond that available at the time of the Glyxambi approval (i.e., the safety database now includes data from two additional phase 3 trials, 1275.9 and 1275.10). However, it is important to note that the safety data from the pivotal study (1275.1) represent longer treatment exposures (52 weeks) that the supportive studies (1275.9 and 1275.10, which were only 24 weeks). For completeness, the Applicant provided individual and pooled analyses of the safety date from these three studies. As the trials differ from one another with respect to design, comparators, and exposures, Dr. Pucino determined that the pooled analyses were not meaningful. For that reason, Dr. Pucino analyzed the results of the studies separately. However, he noted that the nominal results of the pooled analyses were not concerning.

Table 5: Safety Population, Size and Duration of Exposure (Phase 3 Trials)

Phase 3 Trials	Lina 5 mg + Met	Empa 10 mg + Met	Empa 25 mg + Met	Empa 10 mg + Lina 5 mg + Met	Empa 25 mg + Lina 5 mg + Met
Total Number of Subjects — N	**242**	**268**	**253**	**372**	**361**
1275.1— N	132	140	141	136	137
Exposure — days					
Mean (SD)	333.0 (90.5)	329.6 (94.2)	343.5 (72.3)	349.7 (60.5)	338.3 (83.5)
Median	364.5	364.0	364.0	365.0	364.0
Range	(1, 378)	(1, 377)	(1, 378)	(7, 375)	(1, 379)
Total exposure — PY	120.3	126.3	132.6	130.2	126.9
1275.9	110			110	112
Exposure — days					
Mean (SD)	165.9 (22.8)			163.1 (30.3)	166.3 (22.1)
Median	169.0			168.0	169.0
Range	(1, 188)			(1, 183)	(24, 190)
Total exposure — PY	50.0			50.0	50.1
1275.10 — N		128	112	126	112
Exposure — days					
Mean (SD)		162.2 (33.2)	165.9 (25.5)	163.8 (28.1)	165.6 (26.6)
Median		170.0	170.0	170.0	171.0
Range		(6, 193)	(28, 190)	(21, 184)	(43, 198)
Total exposure — PY		56.8	50.9	56.5	50.8

Source: FDA Clinical Review

Dr. Pucino concluded that the safety profile of Trijardy XR reflects the safety profile of its individual components (i.e., empagliflozin, linagliptin, and metformin). The most common adverse reactions reported in 1275.1 were upper respiratory infections, urinary tract infections, nasopharyngitis, diarrhea, constipation, headache and gastroenteritis. Dr. Pucino concluded that the safety data from the two supportive trials did not identify any new safety concern (see Table 6, Table 7, and his clinical review for additional details).

Table 6: Summary of Common Treatment Emergent Adverse Events (Safety Population)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Subjects with TEAEs — no. (%)	91 (68.9)	96 (68.6)	103 (73.0)	94 (69.1)	98 (71.5)	75 (68.2)	62 (55.4)	57 (51.8)	71 (55.5)	66 (58.9)	61 (48.4)	59 (52.7)
MedDRA Preferred Term	118 (89.4)	124 (88.6)	131 (92.9)	129 (94.9)	126 (92.0)	105 (95.5)	103 (92.0)	106 (96.4)	118 (92.2)	105 (93.8)	111 (88.1)	102 (91.1)
Urinary tract infection	15 (11.4)	13 (9.3)	17 (12.1)	12 (8.8)	12 (8.8)	7 (6.4)	8 (7.1)	3 (2.7)	6 (4.7)	7 (6.3)	10 (7.9)	11 (9.8)
Upper respiratory tract infection	4 (3.0)	11 (7.9)	9 (6.4)	14 (10.3)	11 (8.0)	1 (0.9)	1 (0.9)	3 (2.7)	2 (1.6)	2 (1.8)	0	2 (1.8)
Constipation*	3 (2.3)	3 (2.1)	4 (2.8)	7 (5.1)	8 (5.8)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.9)	1 (0.8)	0
Rate per 100 PY	2.47	2.36	3.01	5.46	6.44	1.94	1.92	1.92	1.69	1.90	1.70	0
Gastroenteritis*	4 (3.0)	2 (1.4)	2 (1.4)	4 (2.9)	8 (5.8)	0	2 (1.8)	3 (2.7)	0	2 (1.8)	2 (1.6)	1 (0.9)
Rate per 100 PY	3.31	1.56	1.50	3.05	6.42	0	3.90	5.82	0	3.82	3.44	1.90
Nasopharyngitis	12 (9.1)	7 (5.0)	5 (3.5)	11 (8.1)	8 (5.8)	8 (7.3)	5 (4.5)	4 (3.6)	3 (2.3)	8 (7.1)	8 (6.3)	2 (1.8)
Headache	8 (6.1)	10 (7.1)	6 (4.3)	7 (5.1)	7 (5.1)	8 (7.3)	3 (2.7)	2 (1.8)	2 (1.6)	2 (1.8)	4 (3.2)	1 (0.9)
Lipase increased*	2 (1.5)	2 (1.4)	1 (0.7)	0	5 (3.6)	6 (5.5)	4 (3.6)	3 (2.7)	1 (0.8)	7 (6.3)	4 (3.2)	7 (6.3)
Rate per 100 PY	1.63	1.56	0.74	0	3.94	11.95	7.87	5.84	1.69	13.51	6.93	13.68
Diarrhoea	0	6 (4.3)	4 (2.8)	9 (6.6)	3 (2.2)	4 (3.6)	4 (3.6)	3 (2.7)	2 (1.6)	1 (0.9)	0	0

Source: FDA Clinical Review

Table 7: Summary of Adverse Events of Special Interest (Phase 3 Trials)

Trial	1275.1					1275.9			1275.10			
Treatment Arm	Lina 5mg + Met (N=132)	Empa 10mg + Met (N=140)	Empa 25mg + Met (N=141)	Empa 10mg + Lina 5mg + Met (N=136)	Empa 25mg + Lina 5mg + Met (N=137)	Lina 5mg + Met (N=110)	Empa 10mg + Lina 5mg + Met (N=112)	Empa 25mg + Lina 5mg + Met (N=110)	Empa 10mg + Met (N=128)	Empa 25mg + Met (N=112)	Empa 10mg + Lina 5mg + Met (N=126)	Empa 25mg + Lina 5mg + Met (N=112)
Subjects with Events – no. (%)												
Decreased renal function	1 (0.8)	0	0	0	1 (0.7)	1 (0.9)	0	0	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Hepatic injury	0	4 (2.9)	1 (0.7)	0	2 (1.5)	2 (1.8)	0	0	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Pancreatitis	1 (0.8)	0	0	0	0	0	0	0	0	0	1 (0.8)	0
Urinary tract infection	20 (15.2)	16 (11.4)	19 (13.5)	13 (9.6)	14 (10.2)	8 (7.3)	8 (7.1)	4 (3.6)	10 (7.8)	9 (8.0)	12 (9.5)	15 (13.4)
Genital infection	3 (2.3)	11 (7.9)	12 (8.5)	8 (5.9)	3 (2.2)	2 (1.8)	2 (1.8)	5 (4.5)	4 (3.1)	9 (8.0)	3 (2.4)	3 (2.7)
Confirmed hypoglycemia*	3 (2.3)	2 (1.4)	5 (3.5)	3 (2.2)	5 (3.6)	1 (0.9)	0	3 (2.7)	0	3 (2.7)	0	0
Bone fracture	0	0	4 (2.8)	4 (2.9)	1 (0.7)	1 (0.9)	0	0	1 (0.8)	0	0	1 (0.9)
Volume depletion	4 (3.0)	1 (0.7)	2 (1.4)	2 (1.5)	1 (0.7)	0	0	1 (0.9)	1 (0.8)	1 (0.9)	0	0
Malignancy	1 (0.8)	2 (1.4)	2 (1.4)	1 (0.7)	3 (2.2)	1 (0.9)	1 (0.9)	0	0	0	0	0
Hypersensitivity	5 (3.8)	5 (3.6)	4 (2.8)	4 (2.9)	7 (5.1)	2 (1.8)	3 (2.7)	5 (4.5)	1 (0.8)	2 (1.8)	2 (1.6)	1 (0.9)

Source: FDA Clinical Review

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

9. Pediatrics

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. After consultation with the Pediatric Research Committee (PeRC), the division has determined it is appropriate to waive the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable to complete because the number of available patients for who participation in such studies would be appropriate is expected to be very small.

10. Labeling

The labeling for Trijardy XR submitted by the applicant was based on approved labeling for Jardiance (empagliflozin; NDA 204629), Glyxambi (empagliflozin/linagliptin; NDA206073), Tradjenta (linagliptin; NDA 201280), Synjardy (empagliflozin/metformin; NDA 206111), Synjardy XR (empagliflozin/metformin extended release; NDA 208658), and Glumetza (metformin extended release; NDA 021748).

During the review of NDA 212614, it was determined that the labeling for Trijardy XR should be revised to address the following issues:

- The indication should be revised to read "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." This revision reflects a decision to simplify the labeling of FCDPs with a glycemic control indication.
- The statement that "the effectiveness of Trijardy XR on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established" was removed. The statement was removed based on both the findings of EMPA-REG (which found a MACE benefit for empaglifozin) and CARMELINA (which found no effect on MACE for linagliptin).
- The renal dosing information was revised to reflect more recent labeling for metformin and empagliflozin products. The labeling was revised to state:
    - No dose adjustment needed in patients with eGFR $\geq$ 45 ml/min/1.73m^2
    - Do not initiate or continue if eGFR < 45 ml/min/1.73m^2
    - Contraindicate if eGFR < 30 ml/min/1.73m^2
    - Section 8.6 (renal impairment) revised to state "Trijardy XR is contraindicated in patients with severe renal impairment (eGFR less than 30 ml/min/1.73m^2), end-stage renal disease or dialysis."
    - The applicant was requested to make similar updates to the Synjardy and Synjardy XR labels at next opportunity
- The ketoacidosis W&P was updated to reflect an SLC issued October 21, 2019
- The hypoglycemic data in Section 6.1 was simplified to include only clinically meaningful hypoglycemia
- The description of CARMELINA is Section 14.3 was abbreviated.

11. Recommendations

- Recommended Regulatory Action

Approval:

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
01/27/2020 11:50:43 AM