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RESEARCH**

APPLICATION NUMBER:

212614Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	212-614
Submission Date	March 27, 2019
Brand Name	TRIJARDY XR
Generic Names	Empagliflozin/linagliptin/metformin
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
Formulation; Strength	Fixed dose combination (FDC) extended release (XR) oral tablet: 25 mg/5 mg/1000 mg; 12.5 mg/2.5 mg/1000 mg 10 mg/5 mg/1000 mg; 5 mg/2.5 mg/1000 mg
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Executive Summary

The sponsor is seeking US marketing approval for TRIJARDY XR tablets under the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. TRIJARDY XR is a fixed-dose combination (FDC) product of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a biguanide. The FDA approved empagliflozin, linagliptin, and metformin each as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The proposed indication of TRIJARDY XR tablets is adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 212-614's Clinical Pharmacology data submitted on March 27, 2019. OCP/DCP2 finds the Clinical Pharmacology data of NDA 212-614 acceptable to support approval provided the sponsor agrees to the labeling recommendations.

Background

This document reviews the Clinical Pharmacology data of empagliflozin/linagliptin/metformin XR FDC tablet. Empagliflozin/linagliptin/metformin XR FDC tablet's active ingredients are all in the following approved products with similar indications to help improve glycemic control in adults with T2DM (Table 1):

Drug(s)	Strength in mg	Brand Name	NDA	Approval Date
E	10; 25	JARDIANCE	204629	August 1, 2014
E/L	10/5; 25/5	GLYXAMBI	206073	January 30, 2015
E/M	5/500; 5/1000 12.5/500; 12.5/1000	SYNJARDY	206111	August 26, 2015
E/M XR	5/1000; 10/1000 12.5/1000; 25/1000	SYNJARDY XR	208658	December 9, 2016

L	5	TRADJENTA	201280	May 2, 2011
L/M	2.5/500; 2.5/850 2.5/1000	JENTADUETO	201281	January 30, 2012
L/M XR	5/1000; 2.5/1000	JENTADUETO XR	208026	May 27, 2016
M	500; 850; 1000	GLUCOPHAGE	020357	March 3, 1995
M XR	500; 750	GLUCOPHAGE XR	021202	October 13, 2000
M XR	500; 1000	GLUMETZA	021748	June 3, 2005

E: empagliflozin; L: linagliptin; M: metformin
Source: Reviewer's compilation

The sponsor conducted the following bioequivalence (BE) and relative bioavailability studies to support NDA 212614 (Table 2):

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: Clinical Overview, Table 1.4.6.1:1

The sponsor conducted the following Phase 3 clinical efficacy and safety studies to support NDA 212614 (Table 3):

Study	Short description of study design and analysis strategy	Treated patients
Add-on studies¹		
1275.9 _(met+lina5)	24 weeks of double-blind treatment, empa ² vs. placebo, add-on therapy to the DPP-4 inhibitor lina 5 mg and metformin background therapy	332 (double-blind)
1275.10 _(met+empa25)	24 weeks of double-blind treatment, lina ² vs. placebo, add-on therapy to the SGLT-2 inhibitor empa 25 and metformin background therapy	224 (double-blind)
1275.10 _(met+empa10)	24 weeks of double-blind treatment, lina ² vs. placebo, add-on to the SGLT-2 inhibitor empa 10 and metformin background therapy	254 (double-blind)
Factorial design study		
1275.1 _(met)	52 weeks of double-blind treatment, empa/lina FDCs ² vs. individual components ³ on metformin background therapy, primary analysis at Week 24, exploratory analyses at Week 52	686

Source: Clinical Overview, Table 1.4.6.2:1

Review of the Current Submission

For the background of Clinical Pharmacology information on empagliflozin, linagliptin, and metformin, see the following Table 4:

Reviewer, Dr.	Product	NDA	DARRTS Reference ID
Sury Sista	GLYXAMBI	206073	3640237
Ritesh Jain	SYNJARDY XR	208658	4008806
Sang Chung	JENTADUETO XR	208026	3923497

Source: Reviewer's compilation

Formulation

The sponsor developed the following 4 FDC tablet strengths of empagliflozin/linagliptin/metformin XR for once-daily dosing:

- 25 mg/5 mg/1000 mg
- 12.5 mg/2.5 mg/1000 mg
- 10 mg/5 mg/1000 mg
- 5 mg/2.5 mg/1000 mg

Each empagliflozin/linagliptin/metformin FDC XR tablet consists of a 1000 mg metformin XR core tablet coated with (b) (4) the immediate release (IR) drug substances of empagliflozin and linagliptin. The XR technology for the metformin core is based on that used in (b) (4)

The excipients in the triple FDC are the same as those used for SYNJARDY XR and JENTADUETO XR. All 4 tablet strengths of the triple FDC contain (b) (4) the color coating agents differ between tablets.

The 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin and 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin FDC XR tablets assessed in the pivotal BE studies (1361.3 and 1361.11, respectively) were manufactured at the commercial scale and will satisfy the batch size recommendation for the 2014 Bioavailability and Bioequivalence guidance. Study 1361.1's batch size is 1/25 of the commercial scale but it is a pilot relative bioavailability study. Thus, this reviewer did not review Study 1361.1.

The individual 25 mg empagliflozin tablets, 5 mg linagliptin tablets, and 500 mg metformin XR tablets are all US commercial products assessed in Study 1361.3. The individual 10 mg empagliflozin tablets, 5 mg linagliptin tablets, and 500 mg metformin XR tablets are all US commercial products assessed in Study 1361.11.

For the 2 clinical studies (1275.9 and 1275.10), the 25 mg empagliflozin/5 mg linagliptin FDC tablets, 10 mg empagliflozin/5 mg linagliptin FDC tablets, 25 mg empagliflozin tablets, 10 mg empagliflozin tablets, and 5 mg linagliptin tablets are all US-approved formulations from different NDAs owned by the same sponsor.

Metformin is the background drug before the addition of empagliflozin and or linagliptin treatments for the 2 clinical studies (1275.9 and 1275.10). Metformin is available as IR or XR formulations. The Glumetza NDA (021748) established the comparative efficacy and safety between metformin immediate release and XR products.

Mutual Interaction Among the Active Ingredients Upon Oral Administration

Per the product label of empagliflozin, empagliflozin has neither significant mutual interaction with linagliptin nor with metformin. Per the product label of linagliptin, linagliptin has no significant mutual interaction with metformin.

Pivotal BE Studies

The sponsor conducted 2 pivotal fed BE studies (1361.3 and 1361.11) with the same study design. Empagliflozin and linagliptin may be taken with or without food, whereas metformin should be taken with food to improve tolerability. Thus, the triple FDC XR tablets are proposed to be taken with food and the 2 BE studies were conducted under fed condition. In both studies, the sponsor followed the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' for the "high fat and high calorie meal" and the study participants completely consumed the meals prior to drug administration.

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 FDC XR tablet to a 25 mg empagliflozin tablet, a 5 mg linagliptin tablet, and two 500 mg metformin XR tablets. A washout of at least 35 days separated the FDC treatment and individual combination of individual component tablets. The sponsor collected serial plasma samples 72 hours postdose and used validated bioanalytical methods to measure the concentrations of empagliflozin, linagliptin, and metformin in plasma samples. See Attachment for geometric mean plasma empagliflozin, linagliptin, and metformin concentration vs. time plots.

Per the respective individual product labels, the terminal half-life of empagliflozin and metformin is 12.4 and 6.2 hours, respectively. The effective half-life of linagliptin is about 12 hours (the terminal half-life is > 100 hours due to saturable binding of linagliptin to DPP-4). Thus, the 72 hours postdose sampling is reasonable for more than 5 half-lives.

For the dosage form proportionality, GLUMETZA (NDA 21748) showed that a 1000 mg GLUMETZA tablet is BE to 2 of 500 mg GLUMETZA tablets as recorded in:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021748s000_Glumetza_ClinPharmR.pdf.

Also, the 2 BE studies (1276.15 and 1276.28) of SYNJARDY XR (NDA 208658) used the approach of a FDC XR tablet with 1000 mg metformin vs. two 500 mg GLUMETZA tablets

(https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208658Orig1s000ClinPharmR.pdf).

Table 5 shows the statistical results for a 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin XR vs. individual combination of a 25 mg empagliflozin, a 5 mg linagliptin, and two 500 mg metformin XR tablets.

Table 5. Statistical results for a 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin XR vs. free combination of a 25 mg empagliflozin, a 5 mg linagliptin, and two 500 mg metformin XR tablets.

Analyte/ Parameter	Adjusted gMean		Adjusted gMean ratio T/R [%]	Two-sided 90% CI (lower limit, upper limit) [%]	Intra- individual gCV [%]
	FDC (T)	Free combination (R)			
	N=29	N=29			
Empagliflozin					
Primary endpoints					
AUC _{0-tz} [nmol·h/L]	5656.07	5488.31	103.06	(100.36, 105.8)	5.8
C _{max} [nmol/L]	540.01	540.26	99.95	(94.52, 105.70)	12.4
Secondary endpoint					
AUC _{0-∞} [nmol·h/L]	5727.20	5554.37	103.11	(100.38, 105.9)	5.9
Linagliptin					
Primary endpoints					
AUC ₀₋₇₂ [nmol·h/L]	238.84	238.11	100.31	(96.65, 104.10)	8.2
C _{max} [nmol/L]	5.69	5.86	97.17	(92.63, 101.93)	10.6
Secondary endpoint					
AUC _{0-∞} [nmol·h/L]	384.27	394.95	97.30	(91.65, 103.29)	13.2
Metformin					
Primary endpoints					
AUC _{0-tz} [ng·h/mL]	12455.82	12412.57	100.35	(96.11, 104.77)	9.5
C _{max} [ng/mL]	1237.16	1147.88	107.78	(102.52, 113.31)	11.0
Secondary endpoint					
AUC _{0-∞} [ng·h/mL]	12745.62	12724.27	100.17	(95.68, 104.86)	10.1

AUC_{0-tz}: Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
Source: Summary of Biopharmaceutics and Associated Analytical Methods, Table 2.2:1

This reviewer's statistical results for the 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin XR (Study 1361.3) are consistent with the sponsor's results. This reviewer used the Phoenix 64, Build 6.3.0.395 to calculate the geometric mean ratio (GMR) and confidence interval (CI) and observed only slight differences after the decimal point for the estimated GMR and 90% CI but these differences do not alter the results' interpretation.

Study 1361.3 showed that the GMR's 90% confidence CI for a 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin XR to individual combination of a 25 mg empagliflozin, a 5 mg linagliptin, and two 500 mg metformin XR tablets were all within the 80 – 125% BE goalpost for the C_{max}, AUC_{0-tz}, and AUC_{0-∞} of empagliflozin, linagliptin, and metformin (Table 5). Thus, the 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin XR is BE to individual combination of 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 FDC XR tablets to a 10 mg empagliflozin tablet, a 5 mg linagliptin tablet, and four 500 mg

metformin XR tablets. A washout of at least 35 days separated the FDC treatment and individual combination of individual component tablets. The sponsor collected serial plasma samples 72 hours postdose and used validated bioanalytical methods to measure the concentrations of empagliflozin, linagliptin, and metformin in plasma samples. See Attachment for geometric mean plasma empagliflozin, linagliptin, and metformin concentration vs. time plots.

The BE study (1288.11) of JENTADUETO XR (NDA 208026) used the approach of 2 FDC XR tablets with 1000 mg metformin each vs. four 500 mg GLUMETZA tablets
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208658Orig1s000ClinPharmR.pdf.

Table 6 shows the statistical results for two 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR vs. individual combination of a 10 mg empagliflozin, a 5 mg linagliptin, and four 500 mg metformin XR tablets.

Table 6. Statistical results for two 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR vs. individual combination of a 10 mg empagliflozin, a 5 mg linagliptin, and four 500 mg metformin XR tablets.

Analyte/ Parameter	Adjusted gMean		Adjusted gMean ratio T/R [%]	Two-sided 90% CI (lower limit, upper limit) [%]	Intra- individual gCV [%]
	FDC (T) N=27	Free combination (R) N=27			
Empagliflozin					
Primary endpoints					
AUC _{0-tz} [nmol·h/L]	2134.53	2125.57	100.42	(98.17, 102.72)	4.8
C _{max} [nmol/L]	209.67	226.50	92.57	(85.21, 100.57)	17.9
Secondary endpoint					
AUC _{0-∞} [nmol·h/L]	2182.26	2166.54	100.73	(98.33, 103.18)	5.1
Linagliptin					
Primary endpoints					
AUC ₀₋₇₂ [nmol·h/L]	270.19	269.77	100.16	(96.17, 104.31)	8.6
C _{max} [nmol/L]	7.02	7.21	97.33	(89.99, 105.26)	16.9
Secondary endpoint					
AUC _{0-∞} [nmol·h/L]	471.40	455.13	103.57	(96.90, 110.71)	14.3
Metformin					
Primary endpoints					
AUC _{0-tz} [ng·h/mL]	21687.12	22748.21	95.34	(91.58, 99.24)	8.5
C _{max} [ng/mL]	1853.03	1767.69	104.83	(98.56, 111.50)	13.2
Secondary endpoint					
AUC _{0-∞} [ng·h/mL]	22288.72	23280.48	95.74	(92.29, 99.32)	7.8

AUC_{0-tz}: Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
 Source: Summary of Biopharmaceutics and Associated Analytical Methods, Table 2.3:1

This reviewer's statistical results for the 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR tablet (Study 1361.11) are consistent with the sponsor's results.

Study 1361.11 showed that the geometric mean ratios' 90% confidence intervals for two 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR vs. individual combination of a 10 mg empagliflozin, a 5 mg linagliptin, and four 500 mg metformin XR tablets were all within the 80 – 125% BE goalpost for the C_{max} , AUC_{0-tz} , and $AUC_{0-\infty}$ of empagliflozin, linagliptin, and metformin (Table 6). Thus, two 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin XR is BE to individual combination of a 10 mg empagliflozin tablet, a 5 mg linagliptin tablet, and four 500 mg metformin XR tablets.

Bioanalytical Assays

Table 7 summarizes the bioanalytical methods validations for Studies 1361.3 and 1361.11.

Table 7. Summary of bioanalytical methods validations for Studies 1361.3 and 1361.11

	Empagliflozin	Linagliptin	Metformin
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS
Matrix	Plasma	Plasma	Plasma
Sample size, μ L	Not found	150	50 [¥] and 25 [§]
Anticoagulant	K ₃ EDTA	K ₃ EDTA	K ₃ EDTA
LLOQ*	1.11	0.1	5
Linear range*	1.11 – 1110	0.1 – 20	5 – 2500 [¥] and 5 – 5000 [§]
Accuracy (in study), %	± 15	98.1 – 101.5	3 – 4
Precision (in study), %	≤ 15	2.6 – 3.9	3.96 – 5.09
Incurred sample reproducibility $\pm 20\%$	117 out of 120 ISR	115 out of 116 ISR	119 out of 120 ISR
Sample stability	≥ 336 days at $-20\pm 10^\circ\text{C}$	389 days at -20°C	366 days at $-24^\circ\text{C}\pm 6^\circ\text{C}$
Freeze/thaw stability	≥ 6 cycles at $-20\pm 10^\circ\text{C}$	Not found	3 cycles at $-24^\circ\text{C}\pm 6^\circ\text{C}$

*nmol/L for empagliflozin and linagliptin; ng/mL for metformin

[¥] and [§] are for Studies 1361.3 and 1361.11, respectively

Source: Reviewer's compilation

The bioanalytical method validations for empagliflozin, linagliptin, and metformin used in Studies 1361.3 and 1361.11 seem acceptable.

Inspection

Upon request, the Office of Study Integrity and Surveillance conducted the following inspections for Studies 1361.3 and 1361.11 (Table 8):

Inspection	Results	Reviews or Documents
Clinical sites	Data from these sites are reliable to support regulatory decision.	Dr. Xiaohan Cai; DARRTS Reference ID: 4519816
Bioanalytical site	Empagliflozin concentration data are reliable for FDA review.	Dr. Yiyue Zhang; DARRTS Reference ID: 4489092
Bioanalytical site	Linagliptin concentration data inspection is not warranted.	Folaremi Adeyemo; DARRTS Reference ID: 4446885
Bioanalytical site	Metformin concentration data are reliable to support regulatory decision.	Dr. Kara Scheibner; DARRTS Reference ID: 4528736

BE Study Waiver (Biowaiver)

The sponsor conducted the 2 BE studies (1361.3 and 1361.11) as discussed above. The sponsor requested biowaiver for the following middle 2 strengths:

- 10 mg empagliflozin/5 mg linagliptin/1000 mg metformin FDC XR tablets
- 12.5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin FDC XR tablets

See the review of biowaiver in Dr. Hansong Chen's Biopharmaceutics review.

Labeling Recommendations

Strikethrough text means the Applicant's proposed deletion. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the Applicant.*

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of TRIJARDY XR

- Assess renal function prior to initiation of TRIJARDY XR and periodically thereafter [see *Warnings and Precautions (5.1,5.6), Use in Specific Populations (8.5,8.6)*].
- In patients with volume depletion, correct this condition prior to initiation of TRIJARDY XR [see *Warnings and Precautions (5.4), Use in Specific Populations (8.5,8.6)*].

2.2 Dosage

- Individualize the starting dose of TRIJARDY XR based on the patient's current regimen:
 - In patients on metformin HCl, with or without linagliptin, switch to TRIJARDY XR containing a similar total daily dose of metformin HCl and a total daily dose of empagliflozin 10 mg and linagliptin 5 mg;
 - In patients on metformin HCl and any regimen containing empagliflozin, with or without linagliptin, switch to TRIJARDY XR containing a similar total daily dose of metformin HCl, the same total daily dose of empagliflozin and linagliptin 5 mg.
- Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg, linagliptin 5 mg and metformin HCl 2000 mg ^{(b) (4)}
[REDACTED]
- TRIJARDY XR should be taken orally once daily with a meal in the morning.
 - TRIJARDY XR 10 mg/5 mg/1000 mg or TRIJARDY XR 25 mg/5 mg/1000 mg should be taken as a single tablet once daily.
 - TRIJARDY XR 5 mg/2.5 mg/1000 mg or TRIJARDY XR 12.5 mg/2.5 mg/1000 mg should be taken as two tablets together once daily.
- Swallow TRIJARDY XR tablets whole. Do not split, crush, dissolve, or chew. ^{(b) (4)}
[REDACTED]

2.3 Patients with Renal Impairment

No dose adjustment is needed in patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m².

TRIJARDY XR is contraindicated in patients with an eGFR less than ~~45~~30 mL/min/1.73 m² [see *Contraindications (4) and Warnings and Precautions (5.1, 5.6)*].

The change from 45 to 30 mL/min/1.73 m² cutoff for contraindication is consistent with that of GLUCOPHAGE and JARDIANCE labels for severe renal impairment. TRADJENTA does not have a contraindication for renal impairment.

7 DRUG INTERACTIONS

(b) (4)

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion (b) (4)

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

(b) (4)

Inducers of P-glycoprotein or CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. (b) (4) use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer (b) (4).

(b) (4)

Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see *Clinical Pharmacology (12.3)*]. Consider the benefits and risks of concomitant use.

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with TRIJARDY XR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients (b) (4)

Drugs Affecting Glycemic Control

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving TRIJARDY XR, the patient should be closely observed to maintain adequate glycemic control [see *Clinical Pharmacology (12.3)*]. When such drugs are withdrawn from a patient receiving TRIJARDY XR, the patient should be observed closely for hypoglycemia.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving TRIJARDY XR.

(b) (4) **Insulin or Insulin Secretagogues**

Coadministration of TRIJARDY XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

TRIJARDY XR is contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 $\text{mL}/\text{min}/1.73 \text{ m}^2$), end-stage renal disease, or dialysis.

The change from 45 to 30 $\text{mL}/\text{min}/1.73 \text{ m}^2$ cutoff is consistent with that of GLUCOPHAGE and JARDIANCE labels for severe renal impairment. TRADJENTA does not have a contraindication for renal impairment.

Empagliflozin

(b) (4)

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment [see *Warnings and Precautions (5.6)*], volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

(b) (4)

Metformin HCl

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment [see (b) (4) *Warnings and Precautions (5.1)*].

8.7 Hepatic Impairment

(b) (4)

Metformin HCl

Use of metformin HCl in patients with hepatic impairment has been associated with some cases of lactic acidosis. TRIJARDY XR is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.1)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRIJARDY XR

empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin, a (b) (4) biguanide (b) (4).

Empagliflozin

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Linagliptin

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

Metformin HCl

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

12.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively

inhibits DPP-4, but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

12.3 Pharmacokinetics

(b) (4)

Administration of TRIJARDY XR with food resulted in no change in overall exposure of empagliflozin or linagliptin. For metformin extended-release, high-fat meals increased systemic exposure (as measured by area-under-the-curve [AUC]) by approximately 70% relative to fasting, while C_{\max} is not affected. Meals prolonged T_{\max} by approximately 3 hours.

Empagliflozin

Absorption

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{\max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Metabolism

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [¹⁴C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin

Absorption

The absolute bioavailability of linagliptin is approximately 30%. A high-fat meal reduced C_{max} by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin may be administered with or without food.

Distribution

The mean apparent volume of distribution at steady state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Metabolism

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Elimination

Following administration of an oral [¹⁴C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Metformin HCl

Absorption

Following a single oral dose of 1000 mg (2 x 500 mg tablets) metformin HCl extended-release after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1000 mg (2 x 500 mg tablets) dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher C_{max} of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin HCl extended-release from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and C_{max} . Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, (b) (4) Metformin partitions into erythrocytes, most likely as a function of time.

Metabolism

Intravenous single-dose studies in normal subjects demonstrate that metformin (b) (4) does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Elimination

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is (b) (4) via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

TRIJARDY XR: Studies characterizing the pharmacokinetics of empagliflozin, linagliptin, and metformin after administration of *TRIJARDY XR* in renally impaired patients have not been performed (b) (4).

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m²), moderate (eGFR: 30 to less than 60 mL/min/1.73 m²), and severe (eGFR: less than 30 mL/min/1.73 m²) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Linagliptin: An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥ 80 mL/min), 6 patients with mild renal impairment (CrCl 50 to < 80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to < 50 mL/min), 10 patients with type 2 diabetes and severe renal impairment (CrCl < 30 mL/min), and 11 patients with type 2 diabetes and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects.

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased (AUC _{τ ,ss} by 71% and C_{max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor.

Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function. Patients with type 2 diabetes and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes groups, renal excretion was below 7% of the administered dose.

These findings were further supported by the results of population pharmacokinetic analyses.

Metformin HCl: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Hepatic Impairment

TRIJARDY XR: Studies characterizing the pharmacokinetics of empagliflozin, linagliptin, and metformin after administration of TRIJARDY XR in hepatically impaired patients have not been performed.

Empagliflozin: In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75% and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Metformin HCl: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Effects of Age, Body Mass Index, Gender, and Race

Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin [see *Use in Specific Populations (8.5)*].

Linagliptin: Based on the population PK analysis, age, body mass index (BMI), gender and race do not have a clinically meaningful effect on pharmacokinetics of linagliptin [see *Use in Specific Populations (8.5)*].

Metformin HCl: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin HCl in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Limited data from controlled pharmacokinetic studies of metformin HCl in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin, linagliptin, or metformin after administration of TRIJARDY XR in pediatric patients have not been performed.

Drug Interactions

Pharmacokinetic drug interaction studies with TRIJARDY XR have not been performed; however, such studies have been conducted with the individual components of TRIJARDY XR (empagliflozin, linagliptin, and metformin HCl).

Empagliflozin

In vitro Assessment of Drug Interactions

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin also does not inhibit UGT1A1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

(b) (4)
Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes (see Figure 1). (b) (4)

Needles to list, if not clinically relevant. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

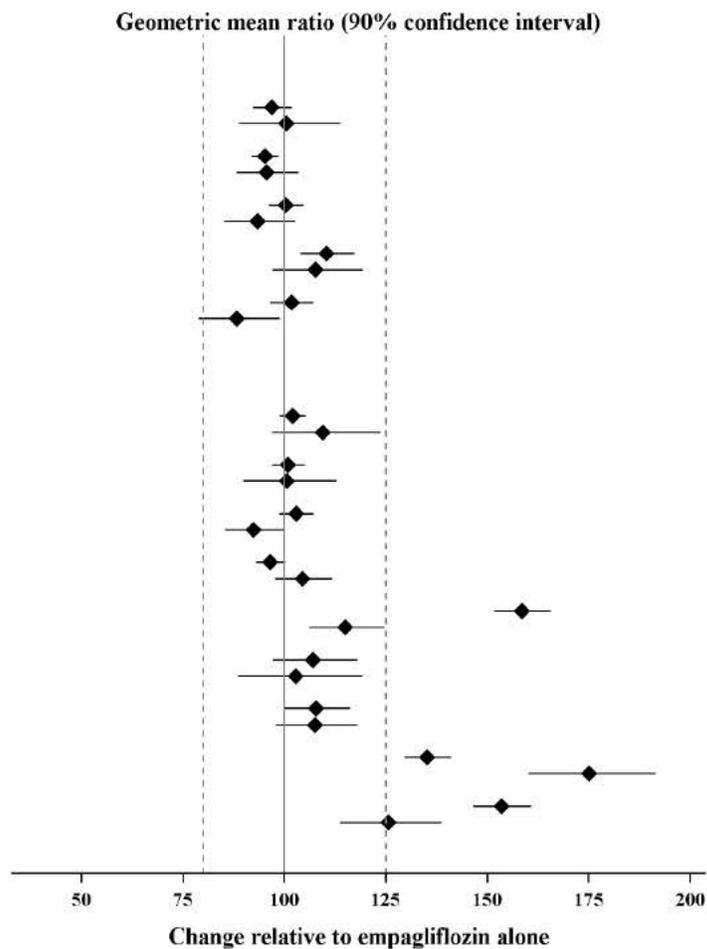
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]

Antidiabetic drugs

Metformin, 1000 mg, twice daily ^a	AUC	
	C _{max}	
Glimepiride, 1 mg, single dose ^{a,e}	AUC	
	C _{max}	
Pioglitazone, 45 mg, once daily ^a	AUC	
	C _{max}	
Sitagliptin, 100 mg, once daily ^a	AUC	
	C _{max}	
Linagliptin, 5 mg, once daily ^a	AUC	
	C _{max}	

Others

Simvastatin, 40 mg, single dose ^b	AUC	
	C _{max}	
Warfarin, 25 mg, single dose ^c	AUC	
	C _{max}	
Verapamil, 120 mg, single dose ^b	AUC	
	C _{max}	
Ramipril, 5 mg, once daily ^c	AUC	
	C _{max}	
Gemfibrozil, 600 mg, twice daily ^b	AUC	
	C _{max}	
Hydrochlorothiazide, 25 mg, once daily ^c	AUC	
	C _{max}	
Torsemide, 5 mg, once daily ^c	AUC	
	C _{max}	
Rifampicin, 600 mg, single dose ^d	AUC	
	C _{max}	
Probenecid, 500 mg, twice daily ^d	AUC	
	C _{max}	



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, single dose; ^cempagliflozin, 25 mg, once daily; ^dempagliflozin, 10 mg, single dose

(b) (4)

Needless to list because it is covered in Section 7.4.

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]

Antidiabetic drugs

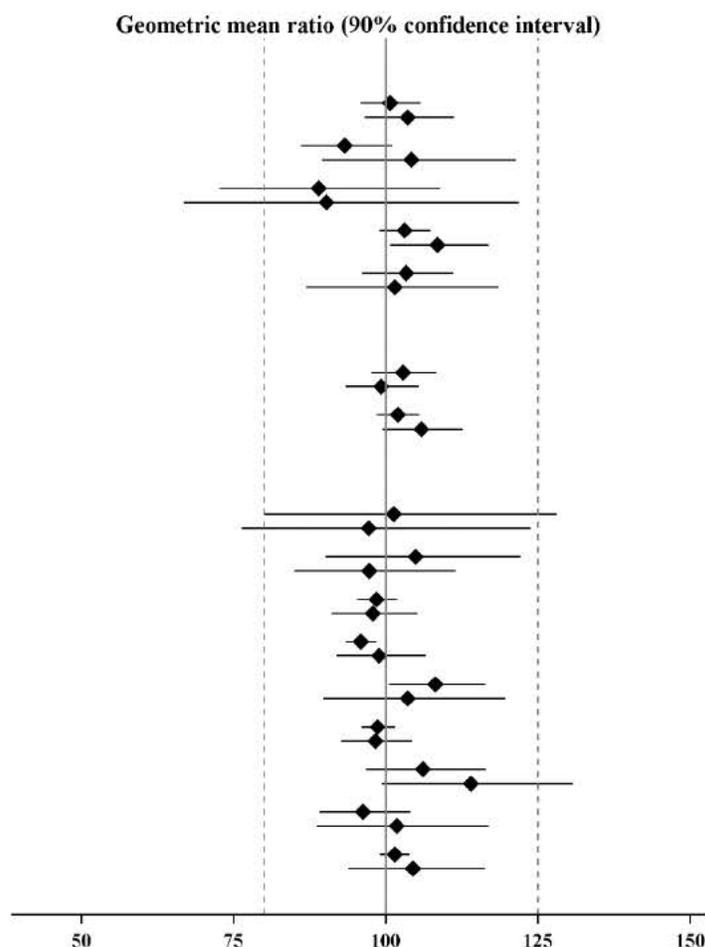
Metformin, 1000 mg, twice daily ^a	AUC C _{max}
Glimepiride, 1 mg, single dose ^{a, (b) (4)}	AUC C _{max}
Pioglitazone, 45 mg, once daily ^b	AUC C _{max}
Sitagliptin, 100 mg, once daily ^a	AUC C _{max}
Linagliptin, 5 mg, once daily ^a	AUC C _{max}

Oral contraceptives

Ethinylestradiol, 30 mcg, once daily ^{b,f}	AUC C _{max}
Levonorgestrel, 150 mcg, once daily ^{b,f}	AUC C _{max}

Others

Simvastatin, 40 mg, single dose ^c	AUC C _{max}
Simvastatin acid ^d	AUC C _{max}
R-Warfarin, 25 mg, single dose ^{b,e}	AUC C _{max}
S-Warfarin, 25 mg, single dose ^{b,e}	AUC C _{max}
Ramipril, 5 mg, once daily ^b	AUC C _{max}
Ramiprilat ^g	AUC C _{max}
Digoxin, 0.5 mg, single dose ^b	AUC C _{max}
Hydrochlorothiazide, 25 mg, once daily ^b	AUC C _{max}
Torsemide, 5 mg, once daily ^b	AUC C _{max}



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, once daily; ^cempagliflozin, 25 mg, single dose; ^dadministered as simvastatin; ^eadministered as warfarin racemic mixture; ^fadministered as Microgynon®; ^gadministered as ramipril

(b) (4)

Linagliptin

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. (b) (4)

In vivo studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT). (b) (4)

Table 3 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug ^a	Dosing of Linagliptin ^a	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0	
			AUC ^e	C _{max}
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide (b) (4)	1.75 mg ^d	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg ^d	2.01	2.96
Rifampin ^c	600 mg QD	5 mg QD	0.60	0.56

^aMultiple dose (steady state) unless otherwise noted

(b) (4)

Needless to list because it is covered in Section 7.4.

^cFor information regarding clinical recommendations [see Drug Interactions (7)(b)(4)].

^dSingle dose

^eAUC = AUC(0 to 24 hours) for single dose treatments and AUC = AUC(TAU) for multiple-dose treatments

QD = once daily

BID = twice daily

TID = three times daily

Table 4 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug ^a	Dosing of Linagliptin ^a	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0		
				AUC ^d	C _{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide (b) (4)	1.75 mg ^c	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone	0.94	0.86
			metabolite M-III	0.98	0.96
			metabolite M-IV	1.04	1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin	1.34	1.10
			simvastatin acid	1.33	1.21
Warfarin	10 mg ^c	5 mg QD	R-warfarin	0.99	1.00
			S-warfarin	1.03	1.01
			INR	0.93 ^e	1.04 ^e
			PT	1.03 ^e	1.15 ^e
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol	1.01	1.08
			levonorgestrel	1.09	1.13

^aMultiple dose (steady state) unless otherwise noted

Needless to list because it is covered in Section 7.4.

°Single dose

°AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple-dose treatments

°AUC = AUC(0-168) and $C_{max} = E_{max}$ for pharmacodynamic end points

INR = International Normalized Ratio

PT = Prothrombin Time

QD = once daily

TID = three times daily

Metformin HCl

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC [†]	C_{max}
Glyburide (b) (4)	5 mg	500 mg [‡]	metformin	0.98 [‡]	0.99 [‡]
Furosemide	40 mg	850 mg	metformin	1.09 [‡]	1.22 [‡]
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05 [‡]	1.07 [‡]
D Cationic drugs (b) (4) eliminated by renal tubular secretion may (b) (4) metformin elimination [see (b) (4) Drug Interactions (7)(b) (4)]. To be consistent with the GLUCOPHAGE label.					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
C arbonic anhydrase inhibitors may cause metabolic acidosis [see (b) (4) Drug Interactions (7)(b) (4)].					
Topiramate***	100 mg	500 mg	metformin	1.25	1.17

*All metformin and coadministered drugs were given as single doses

†AUC = AUC(INF)

‡Metformin HCl extended-release tablets 500 mg

‡Ratio of arithmetic means

(b) (4)

Needless to list because it is covered in Section 7.4.

***At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC(0-12 hours)

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin HCl*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC [†]	C_{max}
Glyburide (b) (4)	5 mg	500 mg [§]	glyburide	0.78 [‡]	0.63 [‡]
Furosemide	40 mg	850 mg	furosemide	0.87 [‡]	0.69 [‡]
Nifedipine	10 mg	850 mg	nifedipine	1.10 [§]	1.08
Propranolol	40 mg	850 mg	propranolol	1.01 [§]	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97 [¶]	1.01 [¶]
Cimetidine (b) (4)	400 mg	850 mg	cimetidine	0.95 [§]	1.01

* All metformin and coadministered drugs were given as single doses

(b) (4)

(b) (4)

Needless to list because it is covered in Section 7.4.

†AUC = AUC(INF) unless otherwise noted

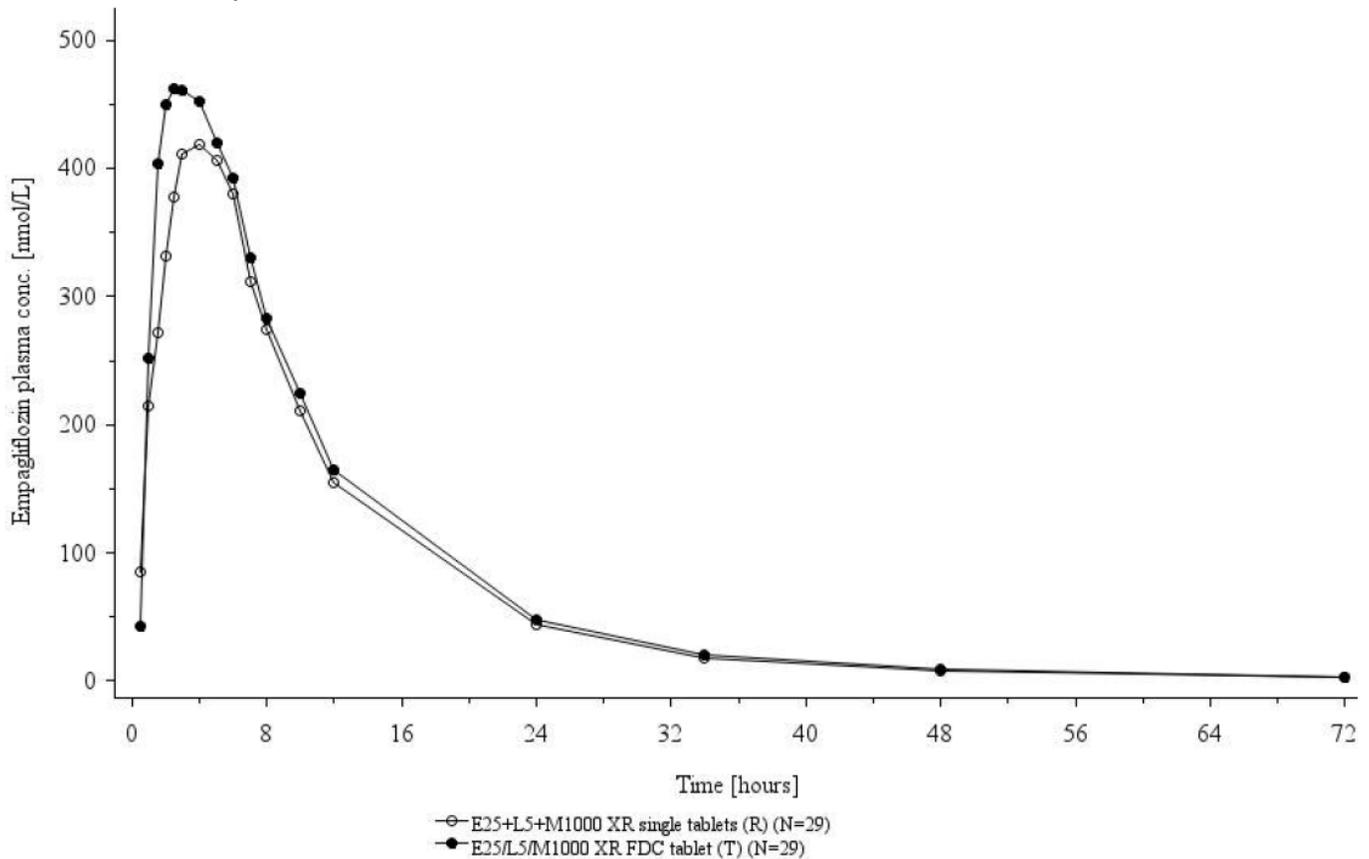
§AUC(0-24 hours) reported

‡Ratio of arithmetic means, p-value of difference <0.05

¶Ratio of arithmetic means

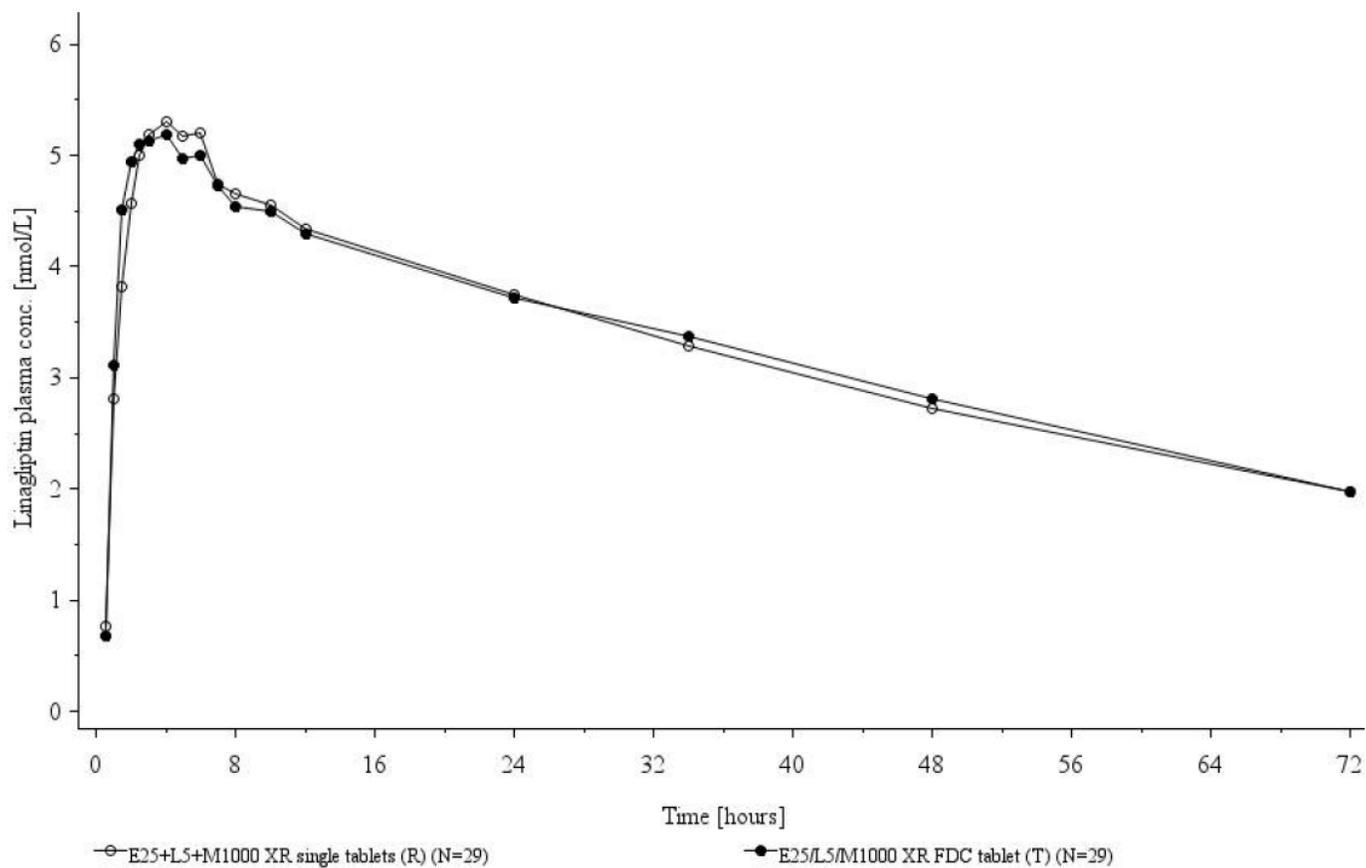
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Geometric mean plasma concentration-time profiles of empagliflozin after single oral administration of 25 mg empagliflozin, 5 mg linagliptin, and 1000 mg metformin XR as FDC or individual combination in fed condition for Study 1361.3.



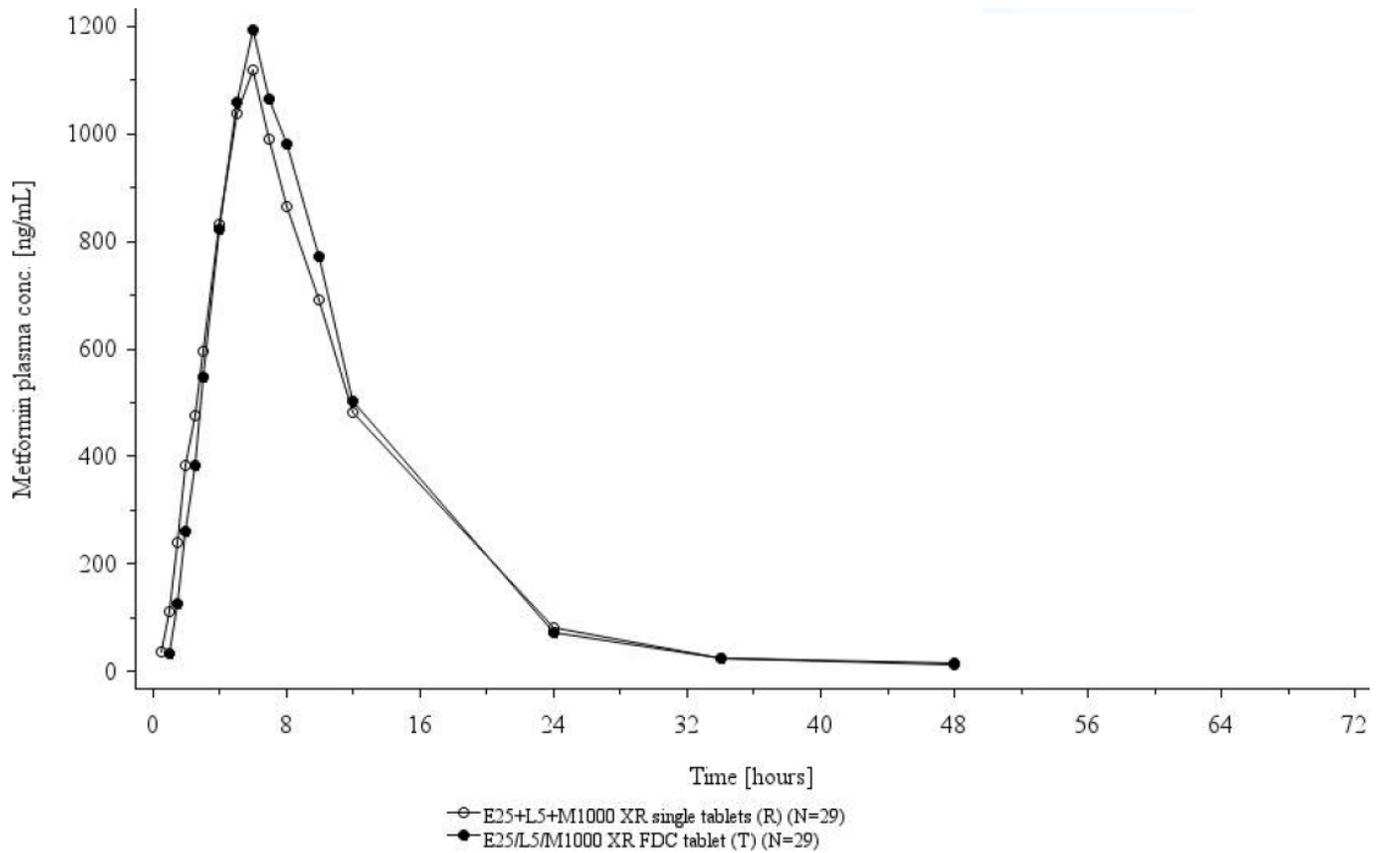
Source: Study 1361.3 report, Figure 11.2.2.1.1: 1

Geometric mean plasma concentration-time profiles of linagliptin after single oral administration of 25 mg empagliflozin, 5 mg linagliptin, and 1000 mg metformin XR as FDC or individual combination in fed condition for Study 1361.3.



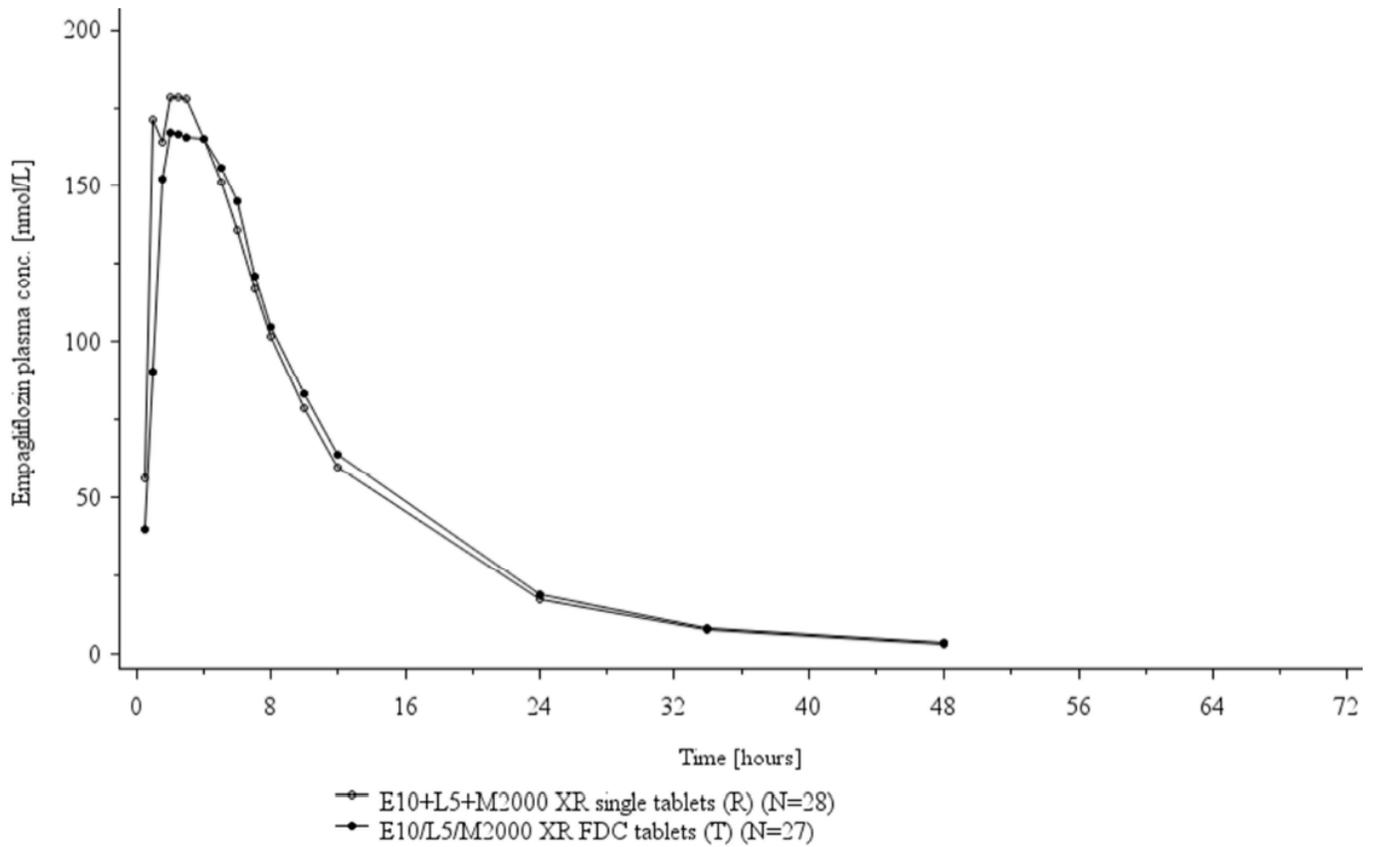
Source: Study 1361.3 report, Figure 11.2.2.2.1: 1

Geometric mean plasma concentration-time profiles of metformin after single oral administration of 25 mg empagliflozin, 5 mg linagliptin, and 1000 mg metformin XR as FDC or individual combination in fed condition for Study 1361.3.



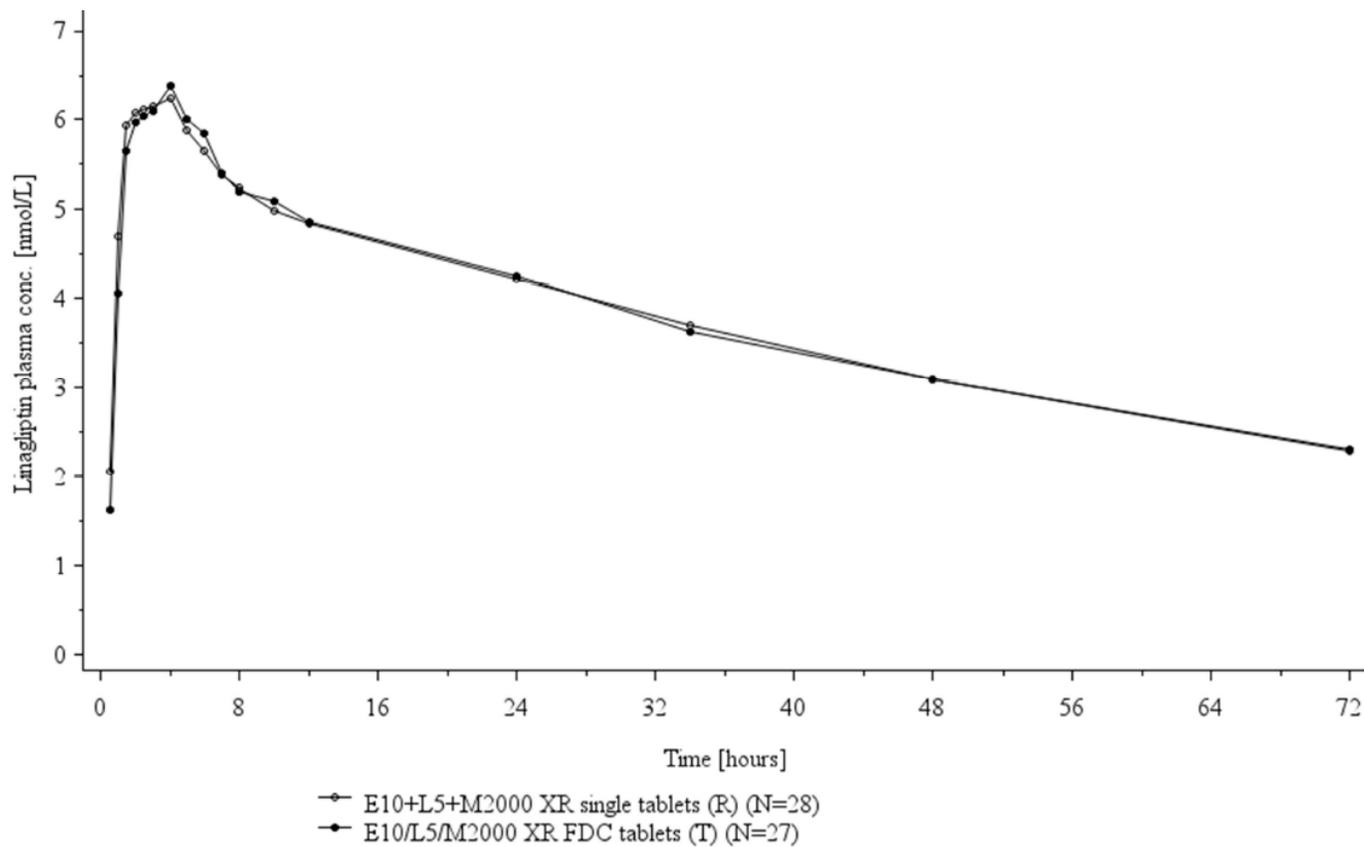
Source: Study 1361.3 report, Figure 11.2.2.3.1: 1

Geometric mean plasma concentration-time profiles of empagliflozin after single oral administration of 10 mg empagliflozin, 5 mg linagliptin, and 2000 mg metformin XR as 2 FDC tablets or individual combination in fed condition for Study 1361.11.



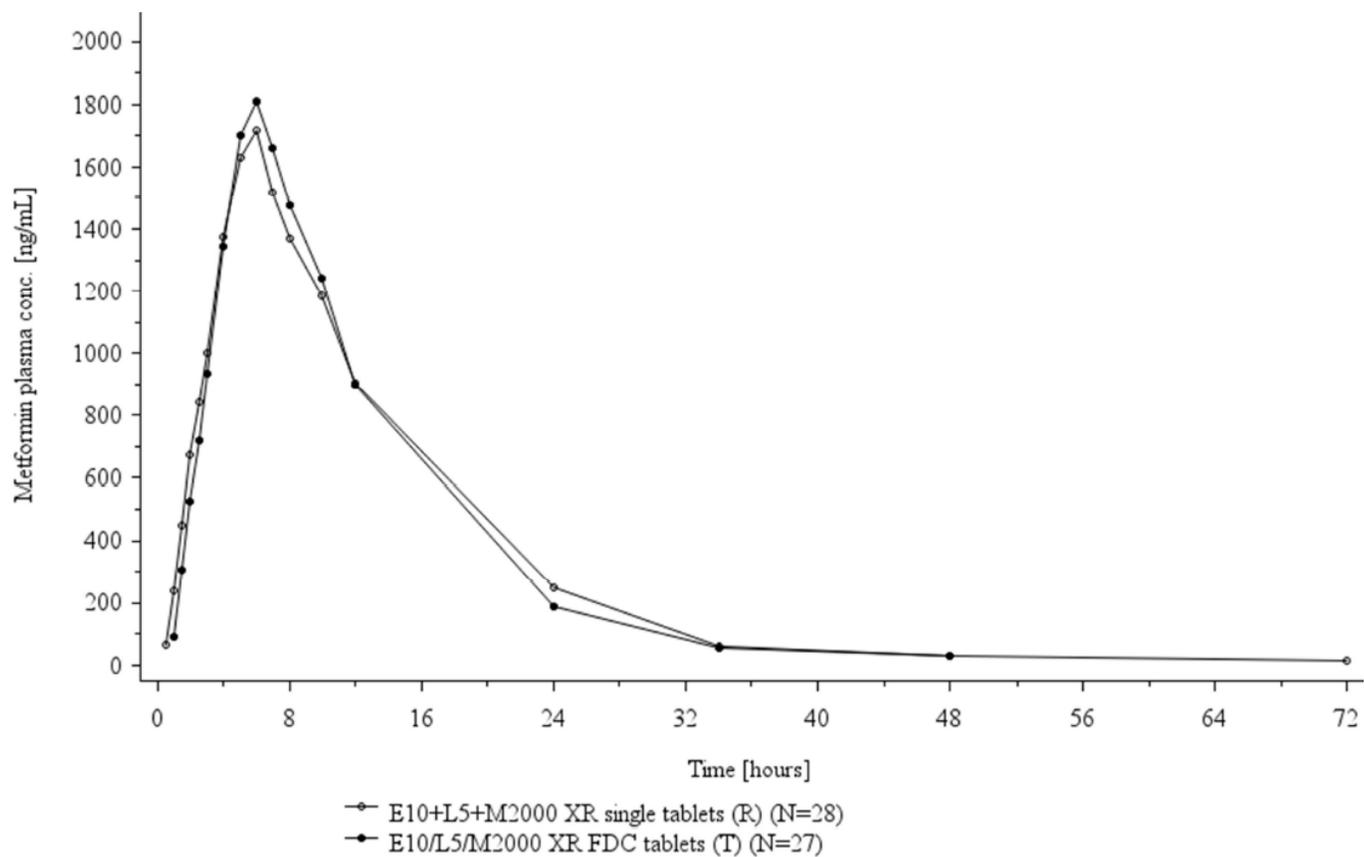
Source: Study 1361.11 report, Figure 11.2.1.1.1: 1

Geometric mean plasma concentration-time profiles of linagliptin after single oral administration of 10 mg empagliflozin, 5 mg linagliptin, and 2000 mg metformin XR as 2 FDC tablets or individual combination in fed condition for Study 1361.11.



Source: Study 1361.11 report, Figure 11.2.1.2.1: 1

Geometric mean plasma concentration-time profiles of metformin after single oral administration of 10 mg empagliflozin, 5 mg linagliptin, and 2000 mg metformin XR as 2 FDC tablets or individual combination in fed condition for Study 1361.11.



Source: Study 1361.11 report, Figure 11.2.1.3.1: 1

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