Brand Name[1]: Trijardy XR

Generic Name[1]: empagliflozin, linagliptin, and metformin hydrochloride

Manufacturer[1]: Boehringer Ingelheim Pharmaceuticals, Inc. & Eli Lilly and Company

Drug Class[2,3]: Antidiabetic Agent: combination of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, a dipeptidyl peptidase-4 (DPP-4) inhibitor and a biguanide

Uses[2,3,4]:

Labeled: Type 2 Diabetes Mellitus (T2DM)
Unlabeled: None

Mechanism of Action[1,2,4]: Empagliflozin is an SGLT2 inhibitor that reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, which increases the excretion of urinary glucose. Linagliptin is a DPP-4 inhibitor that slows the inactivation of incretin hormones. It degrades incretion hormones GLP-1 and GIP, increasing the concentration of active incretin hormones which stimulates the release of insulin and decreasing glucagon levels in circulation. Metformin is a biguanide that lowers both basal and postprandial glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose and improves insulin sensitivity.

Pharmacokinetics[1,2,4]:

Absorption/Distribution:

	Empagliflozin	Linagliptin	Metformin
Tmax	1.5 hours	1.5 hours	7-8 hours
Vd	73.8 L	1110 L	654 ± 358 L
T ½	12.4 hours	Terminal: 200 hours Accumulation: 11 hours	Plasma: 6.2 hours Blood: 17.6 hours
Clearance	10.6 L/hour	70 mL/minute	3.5 x greater than CrCl
Protein Binding	86.2%	70-99%	Negligible
Bioavailability		30%	50-60%

Metabolism: Empagliflozin is primarily metabolized by glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8 and UGT1A9. No

major metabolites were detected and the most abundant were three glucuronide conjugates. The majority (90%) of Linagliptin is excreted unchanged meaning that metabolism is a minor elimination pathway. A small fraction is metabolized to a pharmacologically inactive metabolite. Metformin does not undergo hepatic metabolism or biliary excretion.

Elimination: Empagliflozin is primarily eliminated by urine and feces. 95.6% of the drug was eliminated in feces (41.2%) or urine (54.4%). Majority of drug in feces was unchanged and approximately half of the drug was unchanged in urine. The elimination of Linagliptin is primarily through the enterohepatic system (80%) or the urine (5%) within 4 days of administering the drug. Metformin is primarily excreted renally, 90% unchanged within the first 24 hours.

Efficacy:

DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ, Broedl UC. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015 Mar;38(3):384-93. doi: 10.2337/dc14-2364. Epub 2015 Jan 12. Erratum in: Diabetes Care. 2015 Jun;38(6):1173. PMID: 25583754.

Study Design: Phase 3, randomized, double-blind, parallel-group study

Description of Study:

Methods: Patients (n=686) ≥18 years old with BMI < 45kg/m2 and an A1C > 7 but < 10.55 who had been treated with metformin at the maximum dose for > 12 weeks were enrolled in the study. A two-week placebo run in period was used and then patients were randomized 1:1:1:1:1 to receive empagliflozin/linagliptin 25mg/5mg as a fixed-dose combination (FDC) tablet (n=137), empagliflozin/linagliptin 10mg/5mg FDC tablet (n=136), empagliflozin 25mg tablet (n=141), empagliflozin 10mg tablet (n=140) or linagliptin 5mg tablet (n=132) for 52 weeks as an add-on to their current metformin therapy. All tablets were taken once daily in the morning. The primary outcome of the study was change from baseline in HbA1c at week 24 and the proportion of patients with baseline HbA1c > 7% who had HbA1c < 7% at week 24. Safety outcomes were vital signs, clinical laboratory parameters and AEs.

Results: Reductions from baseline in HbA1c were significantly greater with empagliflozin/linagliptin compared to monotherapy with the individual components. Significantly more patients in the empagliflozin/linagliptin groups reached an HbA1c of < 7% at week 24 compared to patients in the other groups. Additionally, reductions in fasting blood glucose (FBG) at week 24 were significantly greater with the combination therapy than monotherapy with either empagliflozin or linagliptin. Significant reductions in HbA1c with the combination therapy were sustained up to week 52 as well. All reported AEs were mild-moderate in nature and similar across all groups.

Limitations: The lack of a placebo arm means that the additive efficacy of empagliflozin/linagliptin compared with the individual components cannot be conclusively assessed. However, the change from baseline HbA1c would likely be very small with placebo.

Conclusion: Combination empagliflozin/linagliptin is safe and effective as an add-on therapy to metformin in patients with HbA1c > 7. The combination resulted in a significant reduction in HbA1c and FBG levels at week 24 that was also sustained until week 52. Additionally, the use of empagliflozin has been known to cause weight loss in patients. However, these agents pose a small risk of hypoglycemia when combined. In conclusion, empagliflozin/linagliptin added to metformin provides a greater glucose-lowering effect that the individual medications alone. The combination therapy also was well tolerated with minor AEs, showing its safety. This study suggest that triple therapy may be an option for T2DM patients who have failed metformin alone or dual therapy with metformin and may provide a greater advantage over the current guideline approach.

Tinahones FJ, Gallwitz B, Nordaby M, Götz S, Maldonado-Lutomirsky M, Woerle HJ, Broedl UC. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes Obes Metab. 2017 Feb;19(2):266-274. doi: 10.1111/dom.12814. Epub 2016 Nov 24. PMID: 27762093.

Study Design: Two 24-week, phase 3, randomized, double-blind, double-dummy, parallel-group studies

Description of Study:

Methods: Patients with HbA1c between 8 and 10.5% who were receiving a stable dose of metformin at maximum dose for at least 12 weeks were randomized to receive either open-label empagliflozin 10mg (n=352) (study 1) or open-label empagliflozin 25mg (n=354) (study 2) for 16 weeks as add on to their current metformin regimen. During week 17, a 1-week open-label placebo was added to open-label empagliflozin and metformin. After this on-week period, patients with HbA1c between 7 and 10.5% (n=482) were then randomized to receive the double-blind, double-dummy treatment for 24 weeks. Patients in study 1 (n=256) were randomized 1:1 to receive placebo plus empagliflozin/linagliptin 10mg/5mg FDC tablet or placebo plus empagliflozin 10mg tablet. The patients in study 2 (n =226) received placebo plus FDC empagliflozin/linagliptin 25mg/5mg or placebo plus empagliflozin 25mg. In both studies, all treatment groups were also continued on metformin. The primary outcome measure was change from baseline in HbA1c after 24 weeks. The most important secondary outcome was change from baseline in FBG at week 24. Safety endpoints were also assessed.

Results: Linagliptin significantly reduced mean HbA1c change from baseline as add-on therapy to empagliflozin 10 or 25 mg and metformin compared to the placebo groups. Adjusted mean change (SE) in HbA1c (95% CI) from baseline

with linagliptin vs placebo was −0.32% (−0.52%, −0.13%) (−3.59 [−5.71, −1.47] mmol/mol) (P = 0.001) for patients on empagliflozin 10mg and metformin, and −0.47% (−0.66−0.28) (−5.15 [−7.20, −3.10] mmol/mol) (P < 0.001) for patients on empagliflozin 25mg and metformin. Linagliptin also significantly reduced FBG levels from baseline at week 24 with triple therapy compared to placebo/empagliflozin. AEs were lower in the linagliptin as add-on therapy to empagliflozin and metformin compared to the placebo group.

Limitations: There appear to have been some conflicts of interest within the study. In addition to the use of SE (instead of SD) in some of the outcome measures, the study was funded by Boehringer Ingelheim and Eli Lilly and Company which were both manufacturers of Trijardy XR. Additionally, several authors had affiliations with the manufacturers of the drug. Some had served as consultants and others were employees of Boehringer Ingelheim. These potential conflicts of interest could have resulted in the study results being skewed to show that this product was effective based on the author affiliations with the manufacturers.

Conclusion: The results of this randomized, double-blind, controlled trial show that linagliptin in addition to empagliflozin and metformin significantly reduce HbA1c and FBG levels compared to placebo & monotherapy alone. Moreover, the added benefit of weight loss with these medications can further help with glycemic control. This study also showed that the addition of linagliptin to empagliflozin 10 mg or 25 mg and metformin is well tolerated and safe for use.

Søfteland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutomirsky M, Broedl UC. Empagliflozin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Linagliptin and Metformin: A 24-Week Randomized, Double-Blind, Parallel-Group Trial. Diabetes Care. 2017 Feb;40(2):201-209. doi: 10.2337/dc16-1347. Epub 2016 Dec 2. PMID: 27913576.

Study Design: 24-week, phase 3, randomized, double-blind, double-dummy, parallel-group study

Description of Study:

Methods: Patients were enrolled in this study if they had HbA1c between 8% and 10.5% and were receiving a stable maximum dose of metformin for at least 12 weeks. Patients (n=606) were treated with open label linagliptin for 16 weeks as add on therapy to current metformin regimen. A 1-week period then followed during which open-label placebo was added to the linagliptin and metformin. Patients with HbA1c from 7.0% to 10.5% after week 17 were randomized 1:1:1 to FDC empagliflozin/linagliptin 10mg/5mg (n=112), or FDC empagliflozin/linagliptin 25mg/5mg (n=111), or placebo + linagliptin 5mg (n=110) for 24 weeks (in addition to metformin). The primary outcome measure was change from baseline in HbA1c after 24 weeks of treatment. Key secondary outcome was change from baseline in FBG. Safety assessments were also performed.

Results: Empagliflozin 10 mg and 25 mg significantly reduced the mean HbA1c from baseline at week 24 compared to placebo. The adjusted mean differences in change from baseline in HbA1c with empagliflozin 10 and 25 mg versus placebo were −0.79% (95% CI −1.02, −0.55) (−8.63 mmol/mol [−11.20, −6.07 mmol/mol]) and −0.70% (95% CI −0.93, −0.46) (−7.61 mmol/mol [−10.18, −5.05 mmol/mol]), respectively (both $P < 0.001$). Both doses of empagliflozin also significantly reduced mean FBG levels, as well as weight compared to placebo. Empagliflozin in addition to linagliptin and metformin was also shown to be safe; more patients in the placebo group experienced AEs than in the empagliflozin group.

Limitations: In addition to the short length of exposure to the medications and the follow-up period to assess for AEs, the authors identified the small sample size as a limitations of the study.

Conclusion: This phase 3 trial showed that empagliflozin in addition to linagliptin and metformin is safe and effective for T2DM patients for whom glycemic control was not achieved with metformin alone, or metformin in combination with other antidiabetic medications. There were significant reductions in both HbA1c and FBG with the combination therapy compared to placebo. Additionally, this combination therapy can lead to weight loss which can help improve glycemic control. Combination therapy was deemed safe and it has a low risk of hypoglycemic episodes. Empagliflozin 10 mg or 25 mg added on to linagliptin and metformin is safe and effective and can be considered for patients with uncontrolled T2DM for its glycemic effects as well as weight loss and low risk of hypoglycemia.

Contraindications[1,2,3,4]:

Severe Renal Impairment: Trijardy XR is contraindicated in patients with GFR < 30 ml/min/1.73 m^2, end-stage renal disease or dialysis. Assess renal function before therapy initiation and periodically while on therapy. Patients with renal impairment are at an increased risk for lactic acidosis.

Acute or Chronic Metabolic Acidosis, including Diabetic Ketoacidosis: Trijardy XR is contraindicated in patients with diabetic ketoacidosis as well as for Type 1 diabetics. SGLT2 inhibitors are known to cause an increased risk of ketoacidosis. Before initiating therapy with Trijardy, consider factors that may predispose patients to ketoacidosis, including pancreatic insulin deficiency, caloric restrictions, and alcohol abuse.

Hypersensitivity to empagliflozin, linagliptin, metformin of any component of the product: Trijardy XR is contraindicated in patients with a known hypersensitivity to any of the drugs or excipients in Trijardy. Events have included anaphylaxis, urticaria, angioedema, exfoliative dermatitis or other severe allergic skin condition like a serious rash, or bronchial hypersensitivity.

Precautions[1,3,4]:

Lactic Acidosis: Cases of metformin-associated lactic acidosis have been reported. Patients and their families should be educated on the symptoms of lactic acidosis and

what to do if these symptoms occur. Prompt discontinuation of Trijardy XR should occur if lactic acidosis is suspected and supportive measures should be instituted. Patients should be aware of the risk factors associated with lactic acidosis and ways to manage them.

Pancreatitis: Cases of pancreatitis and even fatal pancreatitis have been reported with the use of linagliptin. Patients should be instructed of the signs and symptoms of pancreatitis and if suspected, Trijardy XR should be discontinued and appropriate management be started. Whether or not those with previous cases of pancreatitis are at risk of subsequent pancreatitis is unknown.

Heart Failure: The association between DPP-4 Inhibitors and heart failure has been evaluated in cardiovascular trials. The risks and benefits of Trijardy XR for use in patients at risk for heart failure should thoroughly be considered. Signs and symptoms of heart failure should be explained to patients and if developed, discontinuation of medication should be considered.

Hypotension: Hypotension may occur after administration of empagliflozin especially in those with renal impairment, older patients and those on diuretics. Volume status should be evaluated and corrected before initiation of Trijardy XR and patients should monitor for signs and symptoms of hypotension while on therapy.

Acute Kidney Injury: Empagliflozin is associated with intravascular volume contraction that can lead to acute renal impairment. Factors that may predispose patients to AKI should thoroughly be evaluated before initiation of Trijardy XR.

Urosepsis and Pyelonephritis: Reports of serious urinary tract infections (UTIs) have been seen in patients receiving SLGT2 inhibitors. Patients should be counseled on the signs and symptoms of UTIs and be treated promptly if needed.

Hypoglycemia w/ Insulin & Insulin Secretagogue Use: The use of empagliflozin and linagliptin in combination with sulfonylureas or insulin is associated with higher rates of hypoglycemia. Lower doses of sulfonylureas or insulin may be needed once Trijardy XR is initiated.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Reports have been identified for Fournier's Gangrene with the use of SGLT2 inhibitors in both males and females, along with serious outcomes. Patients should be instructed to watch out for signs and symptoms and if suspected, Trijardy should be discontinued and the patient be treated with broad-spectrum antibiotics.

Genital Mycotic Infections: Empagliflozin increases the risk of genital mycotic infections and those with prior infections are more likely to develop one. Patients should be monitored and treated appropriately.

Vitamin B12 Deficiency: Patients with inadequate vitamin B12 or calcium intake or absorption are at risk of metformin-induced vitamin B12 deficiency. Hematologic parameters should be measured on an annual basis and vitamin B12 every 2-3 years for patients treated with Trijardy XR.

Severe and Disabling Arthralgia: Reports have been identified in patients taking DPP-4 inhibitors. If severe joint pain occurs in patients on Trijardy XR, the DPP-4 inhibitor may be the cause and discontinuation of the drug relieves symptoms.

Bullous Pemphigoid: Reports were identified in those patients being treated with linagliptin, as well as serious cases. Patients taking Trijardy XR should report symptoms such as blisters or erosions and discontinue the drug. Referral should be made to a dermatologist for evaluation and treatment if suspected.

Adverse effects[2,4]:

Common: > 10%

Cystitis (7.6% to 12.5%)
Diuresis (>10%)
Infection (1.6% to 12.5%)
Upper respiratory tract infection (8% to 10.3%)
Urinary tract infection (9.6% to 10.2%)

Infrequent: 1-10%

Abdominal Pain (>5%) | Arthralgia (2.3% to 2.4%) | Balanitis (1.6% to 3.1%) | Candidiasis (1.6% to 6.4%) | Constipation (5.1% to 5.8%) | Cough (<2.1%) | Dehydration (1.1%) | Diarrhea (>5%) | Flatulence (>5%) | Gastroenteritis (3% to 6%) | Headache (5.1%) | Hypercholesterolemia (4.6% to 6.5%) | Hyperlipidemia (2.9% to 3.9%) | Hypoglycemia (0.7% to 3.6%) | Hypotension (1.1%) | Hypovolemia (1.1%) | Increased urinary frequency (3.2% to 3.4%) | Malaise (1% to 5%) | Nausea (> 5%) | Orthostatic hypotension (1.1%) | Pharyngitis (5.8% to 8.1%) | Polydipsia (1.5% to 1.75) | Polyuria (3.2% to 3.4%) | Vaginitis (3.7% to 6.4%) | Vitamin B12 deficiency (7%) | Vomiting (>5%)

Rare: < 1% but Severe

Lactic Acidosis (<0.1%) | Megaloblastic Anemia (>1%) | Pancreatitis (<0.3%)
Phimosis (<0.1%)

Drug Interactions[1]:

Carbonic Anhydrase Inhibitors:

Topiramate or other carbonic anhydrate inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may increase the risk of lactic acidosis.

Drugs that Reduce Metformin Clearance: organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin could increase exposure to metformin and subsequently risk of lactic acidosis.

Alcohol:

Alcohol is known to increase the effect of metformin on lactate, advise patients to avoid excessive alcohol intake while on Trijardy XR.

Diuretics:

Coadministration with diuretics results in increased urine volume and frequency of voids, may lead to volume depletion.

Insulin or Insulin Secretagogues:

Concomitant use may increase the risk of hypoglycemia. Coadministration may require lower doses of insulin or insulin secretagogue to reduce the risk.

Drugs Affecting Glycemic Control: thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid

Drugs that tend to produce hyperglycemia may lead to loss of glycemic control. Coadministration with these drugs should be monitored closely to maintain adequate glycemic control.

Positive Urine Glucose Test:

Urine glucose excretion may increase and can lead to positive urine glucose tests.

Interference with 1,5-AG Assay:

Measurements are unreliable in assessing glycemic control in patients taking SLGT2 inhibitors.

Inducers of P-glycoprotein or CYP3A4 Enzymes

Efficacy may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer.

Dosing/Administration[1,2,3,4]: Dosing should be individualized based on the patient's current regimen:

Adult Dosing:

Treated with metformin, with or without linagliptin: Start with a similar total daily dose of metformin, plus empagliflozin 10 mg/linagliptin 5 mg orally once daily with morning meal, adjust dosing as appropriate

Treated with metformin and empagliflozin, with or without linagliptin: Start with a similar total daily dose of metformin plus current daily dose of empagliflozin and linagliptin 5 mg orally once daily with morning meal

Maximum Dose: empagliflozin 25 mg/linagliptin 5 mg/metformin 2000 mg

Pediatric Dosing:

Safety and efficacy have not been established for use in pediatric or adolescent patients.

Geriatric Dosing:

Start at the low end of dosing range due to metformin component. Same maximum dose as adult dosing. Risk of lactic acidosis increases with age.

Renal Impairment Dosing:

Estimated GFR $\geq$ 45 ml/min/1.73 m^2: No dosage adjustment necessary.
Estimated GFR 30 to < 45 ml/min/1.73 m^2: Do not initiate Trijardy XR in these patients. In patients currently on therapy, discontinue if eGFR is persistently less than 45 ml/min/1.73 m^2
Estimated GFR < 30 ml/min/1.73 m^2: Use is contraindicated.

Hepatic Impairment Dosing:

Use is not recommended in those with hepatic impairment due to increased risk of lactic acidosis secondary to metformin use.

Use in special circumstances[1,2,3,4]:

Pregnancy: There are no adequate and well-controlled studies evaluating the effects of Trijardy XR on human pregnancy and the drug-associated risk of adverse developmental outcomes. There have been animal data showing adverse renal effects with empagliflozin, which may affect renal development and maturation. It is recommended that Trijardy XR not be used during the second and third trimesters of pregnancy and use in the first trimester should be based on benefit/risk assessment.

Lactation: There is limited information regarding the presence of Trijardy XR or its components in human breast milk, the effects on the breastfed infant or the effects on milk production. Metformin is present in breast milk and in animal studies empagliflozin was present in milk of lactating rats. Infant risk cannot be ruled out and due to the potential for serious adverse reactions, breastfeeding during the use of this combination product is not recommended by the manufacturer.

Overdosage: In the event of an overdose with this medication contact the Poison Control Center. Metformin is dialyzable under good hemodynamic conditions so hemodialysis may be useful to remove accumulated drug from patients. Removal of empagliflozin by hemodialysis has not been well studied and the removal of linagliptin is unlikely by both hemodialysis and peritoneal dialysis.

Conclusion[8,9,10,11]:

Trijardy XR is an effective option for patients with T2DM who are inadequately controlled on metformin monotherapy or with dual therapy including metformin. Efficacy studies showed that

the combination of these agents was more effective for lowering HbA1c and FBG levels than the individual drugs themselves. Trijardy XR is a safe medication with a manageable side effect profile. This medication may also help with weight loss which can improve glycemic control as well as increase adherence for those taking multiple medications. In addition to its benefits, Trijardy XR also appears to be cost effective compared to the individual components. The combination tablet, Trijardy XR, costs approximately $555.00 for a 30-day supply. On the other hand, 30 tablets of metformin 1000 mg costs around $15.00-$20.00, but 30 tablets of both empagliflozin and linagliptin cost approximately upwards of $500.00 each. Given its efficacy, tolerability, and additional weight loss and cost benefits, Trijardy XR is an option and appears to have clinical usefulness for uncontrolled T2DM

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