XILINGIO

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

Abbreviated Prescribing information for XILINGIO (Empagliflozin and Linagliptin film-coated Tablets –10 mg/5 mg, 25 mg/5 mg.) [Please refer the complete prescribing information for details].

PHARMACOLOGICAL PROPERTIES:

MECHANISM OF ACTION: ***XILINGIO:*** Xilingio contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor. ***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.

INDICATIONS: XILINGIO is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DOSAGE AND ADMINISTRATION: Once daily in the morning taken with or without food or As directed by the Physician. Tablets should be taken orally.

CONTRAINDICATION: Patients on dialysis, Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in XILINGIO, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred.

WARNINGS & PRECAUTIONS: ***Pancreatitis:*** Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. CARMELINA trial acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin. ***Ketoacidosis:*** Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. XILINGIO is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with XILINGIO who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with XILINGIO may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, XILINGIO should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement. Before initiating XILINGIO, consider factors in the patient history that may

predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing XILINGIO for at least 3 days prior to surgery. ***Volume Depletion:*** Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. ***Urosepsis and Pyelonephritis:*** There have been post marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. ***Bullous Pemphigoid:*** Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. ***Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:*** Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with XILINGIO. ***Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):*** Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with XILINGIO presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue XILINGIO, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control. ***Genital Mycotic Infections:*** Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate. ***Hypersensitivity Reactions:*** There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with XILINGIO. ***Severe and Disabling Arthralgia:*** There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. ***Bullous Pemphigoid:*** Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the CARMELINA trial and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. ***Heart Failure:*** An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class.

DRUG INTERACTIONS: ***Diuretics:*** Co-administration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Insulin or Insulin Secretagogues: The risk of hypoglycemia is increased when XILINGIO is used in combination with insulin secretagogues. ***Positive Urine Glucose Test:*** SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. ***Interference with 1, 5-anhydroglucitol (1, 5-AG) Assay:*** Measurements of 1, 5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. ***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.

ADVERSE REACTIONS: Pancreatitis, Ketoacidosis, Volume Depletion, Urosepsis, Pyelonephritis, Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues Precautions, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), Genital Mycotic Infections, Hypersensitivity Reactions, Severe and Disabling Arthralgia, Bullous Pemphigoid, Heart Failure, Skin reactions (rash, urticaria), Acute kidney injury, Constipation, Mouth ulceration, Stomatitis.

Please email at pv@torrentpharma.com for reporting of any adverse event.

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(Additional information is available on request)