120x280mm

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Diajard-L™

(Linagliptin + Empagliflozin)

Highnoon

COMPOSITION
Diajard-L 5mg/10mg Tablet:
Each film-coated tablet contains:
Linagliptin 5mg
Empagliflozin 10mg

Diajard-L 5mg/25mg Tablet:
Each film-coated tablet contains:
Linagliptin 5mg
Empagliflozin 25mg

DESCRIPTION
Contains combination of linagliptin and empagliflozin. Empagliflozin is an inhibitor of the SGLT2 & linagliptin is DPP-4 inhibitor.

MECHANISM OF ACTION
Empagliflozin is an inhibitor of the SGLT2, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

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.

PHARMACOKINETICS
Empagliflozin
After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. Plasma protein binding was 86.2%. No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates. The primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyl-transferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours. The majority of drug-related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug. It may be administered with or without food.

Linagliptin
Linagliptin has nonlinear pharmacokinetics because of high affinity saturable binding to dipeptidylpeptidase-4 (DPP-4) in plasma and tissue. It is rapidly absorbed from gastrointestinal tract and peak plasma concentration occurs within about 1.5 hours. The absolute bioavailability of linagliptin is about 30%. The mean apparent volume of distribution after an intravenous dose is 1110 litres indicating that linagliptin is extensively distributed to the tissues. Plasma protein binding of linagliptin is concentration dependent; at low concentration it is 99% bound, but at higher concentrations when DPP-4 is fully saturated, 70 to 80% is bound to other plasma proteins and 20 to 30% is unbound.

After multiple oral doses, linagliptin has an accumulation half-life of about 12 hours. Linagliptin is not extensively metabolized. It undergoes biphasic (or possibly triphasic) elimination and at a steady rate has a terminal half-life of more than 100 hours. About 80% is eliminated in the faeces and 5% in the urine.

INDICATIONS AND USAGE
It is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

It is not recommended for use to improve glycaemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. It is also not recommended for use to improve glycaemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m². This combination is likely to be ineffective in this setting based upon its mechanism of action.

DOSAGE AND ADMINISTRATION
Assessment of renal function and volume status is recommended before initiating treatment with this combination. Volume depletion should be rectified prior to starting therapy.

The recommended dosage is of Diajard-L (5mg linagliptin / 10mg empagliflozin) once daily in the morning, taken with or without food. It may be increased to 5mg linagliptin / 25mg empagliflozin once daily for additional glycaemic control.

When it is used in combination with metformin, the metformin dose should be continued. When used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

Patients switching from linagliptin (5mg daily dose) and empagliflozin (either 10mg or 25mg daily dose) to this combination should receive the same daily dose of linagliptin and empagliflozin in the fixed dose combination as in separate tablets.

If a dose is missed, and it is 12 hours or more until the next dose, the dose should be taken as soon as the patient remembers. The next dose should be taken at the usual time. If a dose is missed, and it is less than 12 hours until the next dose, the dose should be skipped and the next dose should be taken at the usual time. A double dose should not be taken to compensate for a forgotten dose.

Withhold this combination for at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. Resume when the patient is clinically stable and has resumed oral intake.

CONTRAINDICATIONS
It is contraindicated in patients:
- on dialysis,
- with a hypersensitivity to linagliptin, empagliflozin, or any of the excipients.
- hypersensitivity to any other Sodium-Glucose-Co-Transporter-2 (SGLT2) inhibitor, to any other Dipeptidyl-Peptidase-4 (DPP-4) inhibitor.

ADVERSE REACTIONS
The combined (linagliptin and empagliflozin) reported adverse effects are; urinary tract infection, nasopharyngitis, upper respiratory tract infection, hypoglycaemia, pancreatitis, volume depletion, urosepsis and pyelonephritis, hypoglycaemia with concomitant use with insulin and insulin secretagogues, lower limb amputation, genital mycotic infection, , severe and disabling arthralgia, bullous pemphigoid, skin reactions (rash, urticaria), urosepsis, pyelonephritis, increased cholesterol, increase haematocrit, acute pancreatitis (including fatal pancreatitis), constipation, stomatitis, mouth ulceration, hypersensitivity reactions including anaphylaxis, angioedema, urticaria, exfoliative skin conditions, necrotising fasciitis of the perineum, (Fournier's gangrene), ketoacidosis, rhabdomyolysis, heart failure and acute kidney injury.

The reported adverse events associated with empagliflozin are; hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, hypoglycaemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, hypersensitivity reactions, increased low-density lipoprotein cholesterol, urinary tract infection (asymptomatic bacteriuria, cystitis), female genital mycotic infection (vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial), increased urination (polyuria, pollakiuria, nocturia), upper respiratory tract infection, dyslipidaemia, arthralgia, male genital mycotic infections (balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection), nausea, volume depletion (blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, syncope), increase in serum creatinine, decreases in eGFR, phimosis, hypoglycaemia, increase haematocrit, angioedema, skin reaction (rash, urticaria) and pruritus generalized.

The reported adverse events associated with linagliptin are; nasopharyngitis, diarrhoea, cough, hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, bronchial hyperreactivity), myalgia, pancreatitis, hypoglycaemia, elevated uric acid, elevated lipase and amylase.

DRUG INTERACTIONS
Diuretics: Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion assess volume status and renal function.

Insulin or Insulin Secretagogues: The risk of hypoglycaemia is increased when this combination is used with an insulin secretagogue (e.g., sulfonylurea) or insulin.

Lithium: Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.

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.

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 glycaemic control in patients taking SGLT2 inhibitors.

Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy of empagliflozin. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to this combination is appropriate.

An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin Cmax increased by 15% and AUC increased by 59% following co-administration.

Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

WARNINGS AND PRECAUTIONS
- In patients with type 1 diabetes mellitus, empagliflozin increases the risk of diabetic ketoacidosis. This combination (linagliptin and empagliflozin) is not indicated for glycaemic control in patients with type 1 diabetes mellitus. There have been reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors including this combination. Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse. Ketoacidosis and glucosuria may persist longer than typically expected. If ketoacidosis is suspected, discontinue this combination, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting it.
- Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue this combination (linagliptin and empagliflozin) and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using this combination.
- Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been 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 m²), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating this combination (linagliptin and empagliflozin) in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating it. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
- There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving empagliflozin. Treatment with empagliflozin increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.
- Insulin and insulin secretagogues are known to cause hypoglycaemia. The risk of hypoglycaemia is increased when this combination is used with an insulin secretagogue (e.g., sulfonylurea) or insulin. Therefore, a lower dosage of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycaemia.
- 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 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 this combination 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 this combination (linagliptin and empagliflozin), closely monitor blood glucose levels, and provide appropriate alternative therapy for glycaemic control.
- 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.
- In some clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. In a long-term cardio-renal outcome trial, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported. Amputation of the toe and mid-foot were noted and some involving above and below the knee. Some patients had multiple amputations. This combination is not indicated for the treatment of chronic kidney disease. Peripheral artery disease, and diabetic foot infection (including osteomyelitis), were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of diabetic foot, peripheral artery disease (including previous amputation) or diabetes. Counsel patients about the importance of routine preventative foot care. Monitor patients for signs and symptoms of diabetic foot infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.
- There have been reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. 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 this combination (linagliptin and empagliflozin). There have been reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue this combination (linagliptin and empagliflozin), treat promptly per standard of care, and monitor until signs and symptoms resolve.
- This combination is contraindicated in patients with hypersensitivity to linagliptin, empagliflozin or any of the excipients.
- There have been reports of severe and disabling arthralgia in patients taking linagliptin. 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 DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.
- Bullous pemphigoid has been reported in patients treated with linagliptin. Cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. Patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving this combination. If bullous pemphigoid is suspected, this combination (linagliptin and empagliflozin) should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.
- 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. Consider the risks and benefits of this combination prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of it.
- Haematocrit increase was observed with empagliflozin treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no data from the use of linagliptin and empagliflozin in pregnant women. Animal studies have shown that linagliptin and empagliflozin cross the placenta during late gestation, but do not indicate direct or indirect harmful effects with respect to early embryonic development with either linagliptin or empagliflozin. As a precautionary measure it is preferable to avoid the use of this combination during pregnancy.

Breast-feeding
No data in humans are available on excretion of linagliptin and empagliflozin into milk. Available non-clinical data in animals have shown excretion of linagliptin and empagliflozin in milk. A risk to newborns or infants cannot be excluded.
This combination (linagliptin and empagliflozin) should not be used during breast-feeding.

Elderly
The safety profile of this combination did not differ in the elderly. Based on empagliflozin experiences, elderly patients may be at increased risk of volume depletion. Renal function and risk of volume depletion should be taken into account in elderly patients.

Paediatric population
Safety and efficacy of this combination in paediatric patients below 18 years of age have not been established. No data are available.

Hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment and therapeutic experience in such patients is limited. Therefore, this combination (linagliptin and empagliflozin) is not recommended for use in this population. In elderly no dose adjustment based on age is required. Based on very limited experience in patients 75 years and older, initiation of this combination is not recommended in this population.

Renal impairment
In patients with an eGFR below 60mL/min/1.73 m² or CrCl less than 60mL/min, the daily dose of linagliptin / empagliflozin is limited to 5mg / 10mg. Linagliptin / empagliflozin is not recommended when eGFR is below 30 mL/min/1.73 m² or CrCl is below 30 mL/min. Linagliptin / empagliflozin should not be used in patients with ESRD or in patients on dialysis. There are insufficient data to support use in these patients.

Assessment of renal function is recommended as follows:
- prior to linagliptin / empagliflozin initiation and periodically during treatment, i.e. at least yearly.
- prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

OVERDOSAGE
Empagliflozin increased urine glucose excretion leading to an increase in urine volume. Removal of empagliflozin by haemodialysis has not been studied, and removal of linagliptin by haemodialysis or peritoneal dialysis is unlikely.

DOSAGE & INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30ºC. Keep in a dry place. Protect from light.

PRESENTATION
Diajard-L 5mg/10mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

Diajard-L 5mg/25mg Tablets:
Alu. Alu. Blister Pack of 2 x 7's.

ڈائیاجارڈ-ایل™

(لینا گلیپٹن + ایمپا گلیفلوزن)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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