1. Generic Name and Brand Name

Empagliflozin 25 mg & Linagliptin 5 mg Tablets

Empexel™-L 25/5

2. Qualitative and quantitative composition

Each film coated tablet contains:

Empagliflozin 25 mg

Linagliptin 5 mg

Colors: Ferric Oxide USP-NF Red & Titanium dioxide IP

Excipients q .s.

3. Dosage form and strength

Refer section 1 & 2

4. Clinical particulars

4.1. Therapeutic indication

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

4.2. Posology and method of administration

Posology

The recommended dose is one tablet daily. Each film coated tablet contains a fixed dose of Empagliflozin and Linagliptin.

If a dose of Empagliflozin and Linagliptin is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Special populations

Renal impairment

The glycaemic efficacy of empagliflozin is dependent on renal function. For cardiovascular risk reduction as add on to standard of care, a dose of 10 mg empagliflozin once daily should be used in patients with an eGFR below 60 ml/min/1.73 m^2 (see Table). Because the glycaemic lowering efficacy of empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered.

For dose adjustment recommendations according to eGFR or CrCL refer to Table.

Table: Dose adjustment recommendations

eGFR [ml/min/1.73 m^2] or CrCL [ml/min]	**Empagliflozin**	**Linagliptin**

60	Initiate with 10 mg. In patients tolerating 10 mg and requiring additional glycaemic control, the dose can be increased to 25 mg.	5mg No dose adjustment for linagliptin is required.
45 to <60	Initiate with 10 mg_ Continue with 10 mg in patients already taking empagliflozin.	
30 to <45	Initiate with 10 mg. Continue with 10 mg in patients already taking empagliflozin.	
<30	Empagliflozin is not recommended.	

Empagliflozin and Linagliptin tablet should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis, as there are insufficient data on empagliflozin to support use in these patients.

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, Empagliflozin and Linagliptin tablet is not recommended for use in this population.

Elderly

No dose adjustment based on age is required. However, renal function and risk of Volume depletion should be taken into account in patients 75 years and older.

Paediatric population

Safety and efficacy of Empagliflozin and Linagliptin tablet in paediatric patients below 18 years of age have not been established. A clinical trial did not establish efficacy of linagliptin in paediatric patients 10 to 17 years of age. Therefore, treatment of children and adolescents with Empagliflozin and Linagliptin tablet is not recommended. Empagliflozin and Linagliptin tablet has not been studied in paediatric patients under 10 years of age.

Method of administration
It should be taken once daily with a meal.

4.3. Contraindication

Hypersensitivity to the active substance or to any of the excipients.

4.4. Special warnings and precautions for use

Empagliflozin
Ketoacidosis

Rare cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl). It is not known if ketoacidosis is more likely to occur with higher doses of empagliflozin.
The risk of ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.
In patients where ketoacidosis is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.
Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal, and the patient's condition has stabilised.
Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.
Patients who may be at higher risk of ketoacidosis include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.
Restarting SGLT2 inhibitor treatment in patients with previous ketoacidosis while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.
Empagliflozin should not be used in patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased ketoacidosis occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.

Renal impairment
For the indication of type 2 diabetes mellitus, in patients with an eGFR below 60 ml/min/1.73 m2or CrCl <60 ml/min the daily dose of empagliflozin is limited to 10 mg. Empagliflozin is not recommended when eGFR is below 30 ml/min/1.73 m^2 or CrCl below 30 ml/min.
For the indication of heart failure, Empagliflozin is not recommended in patients with eGFR <20 ml/min/1.73 m^2.
Empagliflozin should not be used in patients with ESRD or in patients on dialysis. There are insufficient data to support use in these patients.
Monitoring of renal function
Assessment of renal function is recommended as follows:
- Prior to 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.

Risk for volume depletion.
Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.
In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

Elderly
The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors)

Complicated urinary tract infections
Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)
Cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients with diabetes mellitus taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.
Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Empagliflozin should be discontinued, and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

Hepatic injury
Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established.

Elevated haematocrit
Haematocrit increase was observed with empagliflozin treatment.

Chronic kidney disease
There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease (eGFR ≥30 mL/min/1.73 m^2) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin.

Infiltrative disease or Takotsubo cardiomyopathy
Patients with infiltrative disease or with Takotsubo cardiomyopathy have not been specifically studied. Therefore, efficacy in these patients has not been established.

Urine laboratory assessments
Due to its mechanism of action, patients taking Empagliflozin will test positive for glucose in their urine.

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

Lactose
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium
Each tablet contains less than 1 mmol sodium (23 mg), that is to say essentially ‘sodium free’.

<u>Linagliptin</u>
Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis: Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with Linagliptin.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin secretagogues and insulin are known to cause hypoglycemia. The risk of hypoglycemia is increased when Linagliptin is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin.
Hypersensitivity Reactions: There have been post marketing reports of serious hypersensitivity reactions in patients treated with Linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions.

Severe and Disabling Arthralgia: There have been post marketing reports of severe and disabling arthralgia in patients taking Linagliptin.

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.

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.

4.5. Drugs interactions

Empagliflozin

Pharmacodynamic interactions

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin.

Pharmacokinetic interactions

Empagliflozin

Effects of other medicinal products on empagliflozin:

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2.

Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations (Cmax) and a 53% increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

The effect of UGT induction (e.g. induction by rifampicin or phenytoin) on empagliflozin has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Empagliflozin 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. These changes were not considered to be clinically meaningful.

Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in Cmax and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin.

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

Effects of empagliflozin on other medicinal products
Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium. Based on in vitro studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with active substances that are P-gp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in Cmax of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 in vitro at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.
Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

Linagliptin
Drug Interactions with Linagliptin
Inducers of P-glycoprotein and CYP3A4 Enzymes
Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp inducer or CYP 3A4 inducer. As Linagliptin and Metformin Hcl is a fixed-dose combination of linagliptin and metformin, use of alternative treatments (not containing linagliptin) is strongly recommended when concomitant treatment with a strong P-gp or CYP 3A4 inducer is necessary.

Insulin Secretagogues or Insulin
Co-administration of Linagliptin and Metformin Hcl 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.

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 Linagliptin and Metformin Hcl, the patient should be closely observed to maintain adequate glycemic control.

When such drugs are withdrawn from a patient receiving Linagliptin and Metformin Hcl, the patient should be observed closely for hypoglycemia.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Empagliflozin

Renal impairment:

In patients with mild, moderate or severe renal impairment (eGFR <30 to <90 ml/min/1.73 m^2) and patients with kidney failure/end stage renal disease (ESRD), 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. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure.

Hepatic impairment:

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

Body Mass Index:

Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. In this analysis, AUC was estimated to be 5.82%, 10.4%, and 17.3% lower in subjects with BMI of 30, 35, and 45 kg/m^2, respectively, compared to subjects with a body mass index of 25 kg/m^2.

Gender:

Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race:

In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25 kg/m^2 compared to non-Asians with a body mass index of 25 kg/m^2.

Elderly

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Paediatric population

A paediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Pregnancy
There are no data from the use of empagliflozin in pregnant women. Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development. As a precautionary measure, it is preferable to avoid the use of empagliflozin during pregnancy.

Breast-feeding
No data in humans are available on excretion of empagliflozin into milk. Available toxicological data in animals have shown excretion of empagliflozin in milk. A risk to the newborns/infants cannot be excluded. empagliflozin should not be used during breast-feeding.

Fertility
No studies on the effect on human fertility have been conducted for empagliflozin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

Linagliptin
Patients with Renal impairment
Results of study, supported by results of population pharmacokinetic analyses, indicate that no dose adjustment is recommended in patients with renal impairment.

Hepatic Impairment
Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC0-24 and approximately 23% lower Cmax compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition. No dose adjustment of linagliptin is necessary in patients with hepatic impairment.

Gender
No dose adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Geriatric
No dose adjustment is recommended based on age, as age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Pediatric
Studies characterizing the pharmacokinetics of linagliptin in pediatric patients have not yet been performed.

Race
No dose adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of linagliptin based on available pharmacokinetic data, including subjects of White, Hispanic, Black, and Asian racial groups.

Pregnant Women

There are no data from the use of drug in pregnant women. There are no adequate data from the use of linagliptin in pregnant women.

Lactating Women
Available pharmacokinetic data in animals have shown excretion of linagliptin/metabolites in milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7. Effects on ability to drive and use machines.

Medication has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid dizziness while driving and using machines.

4.8. Undesirable effects

Empagliflozin
The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), or very rare (<1/10000), and not known (cannot be estimated from the available data).

Table No: 1 Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled studies and from post-marketing experience.

System organ class	Very common	Common	Uncommon	Rare	Very Rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, Nasopharyngitis Urinary tract infection (including pyelonephritis and urosepsis)		Necrotising fasciitis of the perineum (Fournier's gangrene)	
Immune system disorders			Hypersensitivity Angioedema urticaria		
Metabolism and nutrition disorders		Hypoglycaemia (when used with Sulphonylurea or insulin) Thirst	Diabetic ketoacidosis		
Vascular disorders			Volume depletion		
Respiratory, thoracic and mediastinal disorders		Cough			

Gastrointestinal disorders		Constipation	Pancreatitis	Mouth ulceration	
Skin and Subcutaneous tissue disorders		Pruritus (generalized) Rash	Urticaria Angioedema		
Renal and urinary disorders		Increased urination	Dysuria		Turbulointerstital nephritis
Investigations		Amylase increased Lipase increased	Blood creatinine increased/ Glomerular filtration rate decreased Haematocrit increased. Serum lipids increased.		

Linagliptin:
Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received 5 mg linagliptin in double-blind studies as monotherapy or as add-on therapy are presented in the table below (see table).
The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (1/10), common(1/100 to< 1/10), uncommon(1/1000 to< 1/100), rare(1/10000 to< 1/1000), very rare(< 1/10000) or not known (cannot be estimated from the available data).

Table Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies in clinical trial and from post-marketing experience.

System organ class Adverse reaction	**Frequency of adverse reaction**
Infections and infestations	
Nasopharyngitis	uncommon
Immune system disorders	
Hypersensitivity (e.g. bronchial hyperreactivity)	uncommon
Metabolism and nutrition disorders	
Hypoglycaemia[1]	very common
Respiratory, thoracic and mediastinal disorders	
Cough	uncommon

Gastrointestinal disorders	
Pancreatitis	rare#
Constipation[2]	uncommon
Skin and subcutaneous tissue disorders	
Angioedema*	rare
Urticaria*	rare
Rash*	uncommon
Bullous pemphigoid	rare#
Investigations	
Amylase increased	Uncommon
Lipase increased**	Common

* Based on post-marketing experience

** Based on lipase elevations > 3 × ULN observed in clinical trials

Based on Linagliptin cardiovascular and renal safety study (CARMELINA), see also below

[1]Adverse reaction observed in combination with metformin plus sulphonylurea.

[2]Adverse reaction observed in combination with insulin.

4.9. Overdose

Empagliflozin

In controlled clinical studies single doses of up to 800 mg empagliflozin in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg in humans.

Linagliptin

Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated from patients in whom Linagliptin overdosage is suspected.

5. Pharmacological properties

5.1. Mechanism of action

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD19

Pharmacotherapeutic group: tablets contain 2 oral antihyperglycemic drugs used in the management of type 2 diabetes mellitus.

Mechanism of action

Empagliflozin

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors.

Empagliflozin is a reversible, highly potent (IC50 of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucoses transporters important for glucose transport into peripheral tissues and is 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by diuresis which may contribute to sustained and moderate reduction of blood pressure.

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to: increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart, downregulating of sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values and beneficial effects on cardiac remodeling, filling pressures and diastolic function.

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.

5.2. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03.

Cardiovascular outcome The double-blind, placebo-controlled EMPA-REG OUTCOME study compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with type 2 diabetes and established cardiovascular disease. A total of 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA1c was 8.1%, and 71.5% were male. At baseline, 74% of patients were being treated with metformin, 48% with insulin, and 43% with a Sulphonylurea. About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 m^2, 17.8% of 45-60 ml/min/1.73 m^2 and 7.7% of 30-45 ml/min/1.73 m^2.

Patients with high baseline HbA1c >10%.

In a pre-specified pooled analysis of three phase 3 studies, treatment with open-label empagliflozin 25 mg in patients with severe hyperglycemia (N=184, mean baseline HbA1c 11.15%) resulted in a clinically meaningful reduction in HbA1c from baseline of 3.27% at week 24; no placebo or empagliflozin 10 mg arms were included in these studies.

Body weight

In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin resulted in body weight reduction (-0.24 kg for placebo, -2.04 kg for empagliflozin 10 mg and -2.26 kg for empagliflozin 25 mg) at week 24 that was maintained up to week 52 (-0.16 kg for placebo, -1.96 kg for empagliflozin 10 mg and -2.25 kg for empagliflozin 25 mg).

Blood pressure

The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo-controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic and up to 2 antihypertensive therapies. Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c, and 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring. Treatment with empagliflozin provided reductions in seated SBP and DBP.

Heart failure

Empagliflozin in patients with heart failure and reduced ejection fraction A randomised, double-blind, placebo-controlled study (EMPEROR-Reduced) was conducted in 3730 patients with chronic heart failure (New York Heart Association [NYHA] II-IV) and reduced ejection fraction (LVEF ≤40%) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care heart failure therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalization for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent) and eGFR(CKD-EPI)cr slope of change from baseline were included in the confirmatory testing. Heart Failure therapy at baseline included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (88.3%), beta blockers (94.7%), mineralocorticoid receptor antagonists (71.3%) and diuretics (95.0%). A total of 1863 patients were randomized to empagliflozin 10 mg (placebo: 1867) and followed for a median of 15.7 months. The study population consisted of 76.1% men and 23.9% women with a mean age of 66.8 years (range: 25-94 years), 26.8% were 75 years of age or older. 70.5% of the study population were White, 18.0% Asian and 6.9% Black/African American. At randomization,

75.1% of patients were NYHA class II, 24.4% were class III and 0.5% were class IV. The mean LVEF was 27.5%. At baseline, the mean eGFR was 62.0 ml/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. About half of the patients (51.7%) had an eGFR of ≥60 ml/min/1.73 m^2.

Pharmacodynamic properties
Empagliflozin
Empagliflozin lowers blood glucose levels by preventing glucose reabsorption in the kidneys, thereby increasing the amount of glucose excreted in the urine. It has a relatively long duration of action requiring only once-daily dosing. Patients should be monitored closely for signs and symptoms of ketoacidosis regardless of blood glucose level as empagliflozin may precipitate diabetic ketoacidosis in the absence of hyperglycemia. As its mechanism of action is contingent on the renal excretion of glucose, empagliflozin may be held in cases of acute kidney injury and/or discontinued in patients who develop chronic renal disease.
The overexcretion of glucose creates a sugar-rich urogenital environment which increases the risk of urogenital infections in both male and female patients - monitor closely for signs and symptoms of developing infection.

Linagliptin
Linagliptin binds to DPP-4 in a reversible manner and thus 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.

5.3. Pharmacokinetic properties

Empagliflozin
Absorption
After oral administration, Empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median Tmax of 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 Cmax were 1870 nmol.h/l and 259 nmol/l with Empagliflozin 10 mg and 4740 nmol·h/l and 687 nmol/l with Empagliflozin 25 mg once daily. Systemic exposure of Empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic parameters of Empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in Empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes.
Administration of Empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax by approximately 37%

compared to fasted condition. The observed effect of food on Empagliflozin pharmacokinetics was not considered clinically relevant and Empagliflozin may be administered with or without food.

Distribution
The apparent steady-state volume of distribution was estimated to be 73.8 l based on the population pharmacokinetic analysis. Following administration of an oral [14C]-Empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Biotransformation
No major metabolites of Empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-, 3-, 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
Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of Empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour. The inter-subject and residual variabilities for Empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [14C]-Empagliflozin solution to healthy volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). 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.

<u>Linagliptin</u>
Absorption
The absolute bioavailability of linagliptin is approximately 30%. Following oral administration, plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. However, the prolonged elimination does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and Cmax and AUC increased by a factor of 1.3 at steady-state compared with the first dose. Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.
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.

Excretion

Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

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.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Empagliflozin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development. In long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralization in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralization at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic. In a 2-year carcinogenicity study, empagliflozin did not increase the incidence of tumors in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72-times the maximal clinical AUC exposure to empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (hemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumors in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both tumors are common in rats and are unlikely to be relevant to humans. Empagliflozin did not increase the incidence of tumors in female mice at doses up to 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumors in male mice at 1000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. The mode of action for these tumors is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumors are considered not relevant to humans.

At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered

during the 35 period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit. In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear. In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period.

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35 and 270 times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215 times the clinical dose based on AUC exposure. Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an in vivo micronucleus assay. In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943 times the clinical dose based on AUC exposure).

7. Description

Pink colored, arc triangular, flat faced, bevel-edged, film coated tablets, plain on both sides.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not Applicable

8.2. Shelf-life

Refer pack

8.3. Packaging information

Refer pack

8.4. Storage and handling instructions

Refer pack

9. Patient Counselling Information

What is Empagliflozin and Linagliptin Tablets?

Empagliflozin and Linagliptin Tablets are used in type 2 diabetes mellitus.

When should you not take Empagliflozin and Linagliptin Tablets?

If you are allergic to Empagliflozin and Linagliptin Tablets or any of the other ingredients of this medicine. If you think you may be allergic to Empagliflozin and Linagliptin Tablets or any of the other ingredients of Empagliflozin and Linagliptin Tablets, do not take this medicine and talk to your doctor.

If you have taken too many tablets?
Contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.

If you forget to take Tablet?
If you miss a dose of Tablet, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the dose.

What are the possible side effects of Empagliflozin and Linagliptin Tablets?
Empagliflozin and Linagliptin possible side effects are arthralgia, Urinary tract infection, dizziness, constipation, frequent urination, Genital mycotic infections, Allergic reaction, cough, Nausea, Sore throat, Vaginal yeast infection, Darkened urine, Headache, Hypoglycemia, tiredness and trouble breathing.

10. Details of manufacturer
Refer Pack for manufacturer details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi-421 302, Maharashtra, India.

11. Details of permission or licence number with date
Refer Pack for Permission/License details.

12. Date of revision
Version 1.0 dated 04-Feb-25

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For product complaints and queries please write to
webmasterindia@abbott.com