This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. Name of the medicinal product

Empacoza plus

Empacoza plus

2. Qualitative and quantitative composition

Empacoza plus 10 mg/5 mg film-coated tablets

Each film-coated tablet contains 10 mg Empagliflozin and 5 mg Linagliptin.

Empacoza plus 25 mg/5 mg film-coated tablets

Each film-coated tablet contains 25 mg Empagliflozin and 5 mg Linagliptin.

3. Pharmaceutical form

Film-coated tablet

Empacoza plus 25mg/5mg white to off white round biconvex film coated tablet with white to off white core

Empacoza plus 10 mg /5mg : white round biconvex unscored film coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Empacoza plus, fixed dose combination of empagliflozin and linagliptin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

• to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Empacoza plus do not provide adequate glycaemic control

• when already being treated with the free combination of empagliflozin and linagliptin

4.2 Posology and method of administration

Posology

The recommended starting dose is 1 film-coated tablet of Empacoza plus 10 mg/5 mg (10 mg empagliflozin plus 5 mg linagliptin) once daily.

In patients who tolerate this starting dose and require additional glycemic control , the dose can be increased to 1 film coated tablet of 25 mg empagliflozin plus 5 mg linagliptin once daily

When Empacoza /Linagliptin is 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 (see sections 4.4, 4.5 and 4.8).

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

Special populations

Renal impairment

Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin (see sections 4.4 and 5.1).

• In patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or creatinine clearance (CrCl) ≥60 mL/min, no dose adjustment is required.

• In patients with an eGFR <60 mL/min/1.73 m^2 or CrCl <60 mL/min, empagliflozin /Linagliptin should not be initiated.

• In patients tolerating empagliflozin /Linagliptin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl below 60 mL/min, the dose of empagliflozin /Linagliptin should be adjusted to or maintained at 10 mg empagliflozin plus 5 mg linagliptin once daily.

• When eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl persistently below 45 mL/min, treatment should be discontinued (see sections 4.4, 4.8, 5.1, and 5.2).

• In patients with end-stage renal disease or in patients on dialysis, empagliflozin /Linagliptin should not be used as empagliflozin is not expected to be effective in these patients (see sections 4.4 and 5.2).

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 (see section 5.2). Therefore, empagliflozin /Linagliptin is not recommended for use in this population.

Elderly

No dosage adjustment based on age is required. However, renal function and risk of volume depletion should be taken into account in elderly patients (see sections 4.4 and 4.8). Based on very limited experience in patients 75 years and older, initiation of empagliflozin /Linagliptin therapy is not recommended in this population (see sections 4.4 and 5.2).

Paediatric population

Safety and efficacy of empagliflozin /Linagliptin in paediatric patients below 18 years of age have not been established. No data are available.

Method of administration

empagliflozin /Linagliptin tablets are for oral use and can be taken with or without a meal at any time of the day at regular intervals. The tablets should be swallowed whole with water. 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.

4.3 Contraindications

Hypersensitivity to the active substances, to any other Sodium-Glucose-Co-Transporter-2 (SGLT2) inhibitor, to any other Dipeptidyl-Peptidase-4 (DPP-4) inhibitor, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diabetic Ketoacidosis:

Diabetic ketoacidosis Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients 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 DKA is more likely to occur with higher doses of empagliflozin. The risk of DKA 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 DKA 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

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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 DKA 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 DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved. Empacoza plus should not be used for treatment of patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased DKA occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.

Use with medicinal products known to cause hypoglycaemia

Empagliflozin and linagliptin as single agents showed an incidence of hypoglycaemia comparable to placebo when used alone or in combination with other antidiabetics not known to cause hypoglycaemia (e.g. metformin, thiazolidinediones). When used in combination with antidiabetics known to cause hypoglycaemia (e.g. sulphonylureas and/or insulin), the incidence of hypoglycaemia of both agents was increased (see section 4.8).

There are no data about the hypoglycaemic risk of empagliflozin /Linagliptin when used with insulin and/or sulphonylurea. However, caution is advised when empagliflozin /Linagliptin is used in combination with antidiabetics. A dose reduction of the sulphonylurea or insulin may be considered (see section 4.2 and 4.5).

Acute pancreatitis

Use of dipeptidyl peptidase-4 (DPP-4) inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis.

If pancreatitis is suspected, empagliflozin /Linagliptin should be discontinued; if acute pancreatitis is confirmed, empagliflozin /Linagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Monitoring of renal function

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function (see sections 4.2, 5.1 and 5.2). Therefore, assessment of renal function is recommended:

• prior to empagliflozin /Linagliptin 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.

Use in patients with renal impairment

In patients with an eGFR below 60 mL/min/1.73 m^2 or CrCl <60 mL/min, avoidance, dose adjustment or discontinuation of empagliflozin /Linagliptin may be necessary (for details see section 4.2). empagliflozin /Linagliptin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl is persistenly below 45 mL/min. In patients with end-stage renal disease or in patients on dialysis, empagliflozin /Linagliptin should not be used, as empagliflozin is not expected to be effective in these patients (see section 5.2).

Use in patients at risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure (see section 5.1). 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 (e.g. thiazide and loop diuretics, see also section 4.5) 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 /Linagliptin should be considered until the fluid loss is corrected.

Urinary tract infections

In empagliflozin /Linagliptin clinical trials, the incidence of urinary tract infections was overall similar between the patients treated with empagliflozin /Linagliptin and the patients treated with empagliflozin or linagliptin. The frequencies were comparable to the incidence of urinary tract infections in empagliflozin clinical trials (see section 4.8). In a pool of placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo and higher in patients treated with empagliflozin 10 mg (see section 4.8). Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Pyelonephritis and urosepsis were not reported from the clinical trials in patients treated with empagliflozin /Linagliptin. However, temporary interruption of empagliflozin /Linagliptin should be considered in patients with complicated urinary tract infections.

Necrotizing Fasciitis of perineum (Fournier's Gangrene).

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients 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, Glyxambi 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 ongoing 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.

Genital Mycotic Infections

Empacoza plus increases the risk of genital mycotic infections. Patients who have a history of genital mycotic infections or who are uncircumcised are more likely to develop genital mycotic infections. Monitor and treat appropriately.

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.

Cardiac failure

Experience with empagliflozin in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA

class III-IV. In the EMPA-REG OUTCOME study, 10.1 % of the patients were reported with cardiac failure at baseline. The reduction of cardiovascular death in these patients was consistent with the overall study population.

Urine laboratory assessments

Due to the mechanism of action of empagliflozin, patients taking empagliflozin /Linagliptin 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.

Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment (see section 4.8).

Elderly

A higher risk of volume depletion adverse reactions were reported in patients aged 75 years and older, treated with empagliflozin, especially at 25 mg/day (see section 4.8). 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). Therapeutic experience is limited with empagliflozin /Linagliptin in patients > 75 years of age, and, no experience is available in patients aged 85 years and older. Initiation of therapy with empagliflozin /Linagliptin in this population is not recommended (see section 4.2).

Bullous pemphigoid

Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, empagliflozin /Linagliptin should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed with empagliflozin /Linagliptin and other medicinal products; however, such studies have been conducted with the individual active substances. Based on results of pharmacokinetic studies, no dose adjustment of empagliflozin /Linagliptin is recommended when co-administered with commonly prescribed medicinal products, except those mentioned below.

Pharmacodynamic interactions

Insulin and sulphonylureas

Insulin and sulphonylureas may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or sulphonylureas may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin /Linagliptin (see sections 4.2, 4.4 and 4.8).

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

Empagliflozin is mainly excreted unchanged. A minor fraction is metabolised via uridine 5'-diphosphoglucuronosyltransferases (UGT); therefore, a clinically relevant effect of UGT inhibitors on empagliflozin is not expected (see section 5.2). The effect of UGT induction on empagliflozin has not been studied. Co-administration with known inducers of UGT enzymes should be avoided because of a 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 Glyxambi is appropriate.

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

An interaction study with gemfibrozil, an *in vitro* inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C_{max} 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 C_{max} and a 35 % increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

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.

Effects of empagliflozin on other medicinal products

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.

Effects of other medicinal products on linagliptin

Co-administration of rifampicin decreased linagliptin exposure by 40 %, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-glycoprotein (P-gp) or cytochrome P450 (CYP) isozyme CYP3A4 inducer, particularly if these are administed long-term (see section 5.2). Co-administration with other potent inducers of P-gp and CYP3A4, such as carbamazepine, phenobarbital and phenytoin, has not been studied.

Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and C_{max} of linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1 % at the therapeutic dose of linagliptin, were increased 4 to 5-fold after co-administration with ritonavir. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will be not associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein / CYP3A4 inhibitors.

Interaction studies conducted in healthy volunteers suggest that the pharmacokinetics of linagliptin were not influenced by co-administration with metformin and glibenclamide.

Effects of linagliptin on other medicinal products

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency.

Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin, empagliflozin or oral contraceptives providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

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4.6 Fertility, pregnancy and lactation

The effects of empagliflozin /Linagliptin on pregnancy, breast-feeding and fertility are not known. Effects related to the individual active substances are described below.

Pregnancy

There are no data from the use of empagliflozin and linagliptin in pregnant women.

Breast-feeding

No data in humans are available on excretion of empagliflozin and linagliptin into milk.. A risk to newborns or infants cannot be excluded empagliflozin /Linagliptin should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted with empagliflozin /Linagliptin or with the individual active substances. Non-clinical studies with empagliflozin and linagliptin as single agents do not indicate direct or indirect harmful effects with respect to fertility .

4.7 Effects on ability to drive and use machines

empagliflozin /Linagliptin has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when empagliflozin /Linagliptin is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin and analogues, sulphonylureas).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reaction was urinary tract infection (7.5 % with 10 mg empagliflozin / 5 mg linagliptin and 8.5% with 25 mg empagliflozin / 5 mg linagliptin with (see Description of selected adverse reactions). The most serious adverse reactions were ketoacidosis (< 0.1%), pancreatitis (0.2%), hypersensitivity (0.6%), and hypoglycaemia (2.4%) (see section 4.4).

Overall, the safety profile of empagliflozin /Linagliptin was in line with the safety profiles of the individual active substances (empagliflozin and linagliptin). No additional adverse reactions were identified with empagliflozin / linagliptin.

The adverse reactions shown in the table below (see Table 1) are listed by system organ class and are based on the safety profiles of empagliflozin and linagliptin monotherapy. The information about adverse reactions not reported in Empagliflozin / linagliptin clinical trials is based on the experience from empagliflozin and linagliptin.

Adverse reactions marked with an asterisk (*) are further discussed in section "Description of selected adverse reactions" below.

Tabulated list of adverse reactions

Frequency categories are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1 Adverse reactions

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Urinary tract infection[1,*] (including pyelonephritis and urosepsis)[4]
	Common	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections[1,*]
	Common	Nasopharyngitis[2]
	Not known	Necrotising fasciitis of the perineum (Fournier´s gangrene)[*]
Immune system disorders	Uncommon	Hypersensitivity[2]
	Uncommon	Angioedema[3,4], urticaria[3,4]
Metabolism and nutrition disorders	Common	Hypoglycaemia (when used with sulphonylurea or insulin)[*]
	Common	Thirst
	Rare	Diabetic ketoacidosis[4,#]
Respiratory, thoracic and mediastinal disorders	Common	Cough[2]
Gastrointestinal disorders	Uncommon	Pancreatitis[2]
	Rare	Mouth ulceration[3]
Skin and subcutaneous tissue disorders	Common	Pruritus[1]
	Common	Rash[3,4]
	Not known	Bullous pemphigoid[2,a]
Vascular disorders	Uncommon	Volume depletion[1,*]
Renal and urinary disorders	Common	Increased urination[1,*]
	Uncommon	Dysuria[1]
Investigations	Common	Increased amylase[2]

	Common	Lipase increased[2]
	Uncommon	Haematocrit increased[1,5]
	Uncommon	Serum lipids increased[1,6]
	Uncommon	Blood creatinine increased/Glomerular filtration rate decreased[1,*]
		Muscleskelateal disorders , joint pain (Arthralgia)

[1] derived from empagliflozin experiences

[2] derived from linagliptin experiences

[3] derived from linagliptin postmarketing experience

[4] derived from empagliflozin postmarketing experience

[5] Mean changes from baseline in haematocrit were 3.3% and 4.2% for Empagliflozin /linagliptin 10 mg/5 mg , respectively, compared to 0.2% for placebo. In a clinical trial with empagliflozin, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

[6] Mean percent increases from baseline for for Empagliflozin /linagliptin 10 mg/5 mg versus placebo, respectively, were total cholesterol 3.2% and 4.6% versus 0.5%; HDL-cholesterol 8.5% and 6.2% versus 0.4%; LDL-cholesterol 5.8% and 11.0% versus 3.3%; triglycerides -0.5% and 3.3% versus 6.4 %.

[a] In the CARMELINA study (see section 5.1), bullous pemphigoid was reported in 0.2% patients treated with linagliptin and in no patients treated with placebo.

[#] see section 4.4

Description of selected adverse reactions

Hypoglycaemia

In pooled clinical trials of for Empagliflozin /linagliptin plus in patients with type 2 diabetes and inadequate glycaemic control on background metformin, the frequency of the reported hypoglycaemic events was 2.4 %. The incidence of confirmed hypoglycaemic events was low (< 1,5 %). There was no notable difference of the incidence in patients treated with different dose strengths of empagliflozin /Linagliptin compared to the treatment with empagliflozin or linagliptin.

One patient administered for Empagliflozin /linagliptin experienced a confirmed (investigator-defined), major hypoglycaemic event (defined as an event requiring assistance) in the active- or placebo-controlled trials (overall frequency 0,1 %).

Based on the experience with empagliflozin and linagliptin, an increase of the risk of hypoglycaemia is expected with the concomitant treatment of insulin and /or sulphonylurea (see section 4.4 and information below)

Hypoglycaemia with empagliflozin

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as monotherapy, as add-on to metformin, and as add-on to pioglitazone +/- metformin. The frequency of patients with hypoglycaemia was increased in patients treated with empagliflozin compared to placebo when given as add-on to metformin plus sulphonylurea (empagliflozin 10 mg: 16.1 %, empagliflozin 25 mg: 11.5 %, placebo: 8.4 %), add-on to basal insulin +/- metformin and +/-sulphonylurea (empagliflozin 10 mg: 19.5 %, empagliflozin 25 mg: 28.4 %, placebo: 20.6 % during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg and 25 mg: 36.1 %, placebo 35.3 % over the 78 week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 39.8 %, empagliflozin 25 mg: 41.3 %, placebo: 37.2 % during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 51.1 %, empagliflozin 25 mg: 57.7 %, placebo: 58 % over the 52-week trial).

Major hypoglycaemia with empagliflozin (events requiring assistance)

The frequency of patients with major hypoglycaemic events was low (< 1 %) and similar for empagliflozin and placebo as monotherapy, as add-on to metformin +/- sulfonylurea, and as add-on to pioglitazone +/- metformin.

The frequency of patients with major hypoglycaemic events was increased in patients treated with empagliflozin compared to placebo when given as add-on to basal insulin +/- metformin and +/- sulphonylurea (empagliflozin 10 mg: 0 %, empagliflozin 25 mg: 1.3 %, placebo: 0 % during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 0 %, empagliflozin 25 mg: 1.3 %, placebo 0 % over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 1.6 %, empagliflozin 25 mg: 0.5 %, placebo: 1.6 % during initial 18 weeks treatment when insulin could not be adjusted and over the 52-week trial).

Hypoglycaemia with linagliptin

The most frequently reported adverse event in clinical trials with linagliptin was hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea (22.9 % vs 14.8 % in placebo).

Hypoglycaemias in the placebo-controlled studies (10.9 %; N=471) were mild (80 %; N=384), moderate (16.6 %; N=78) or severe (1.9 %; N=9) in intensity.

Urinary tract infection

In clinical trials with for Empagliflozin /linagliptin, there was no notable difference of the frequency of urinary tract infections in patients treated with for Empagliflozin /linagliptin 10 mg/5 mg: 7.5 %) compared to the patients treated with empagliflozin and linagliptin. The frequencies have been comparable to those reported from the empagliflozin clinical trials (see also section 4.4).

In empagliflozin trials, the overall frequency of urinary tract infection was similar in patients treated with empagliflozin 25 mg and placebo (7.0 % and 7.2 %), and higher in patients treated with empagliflozin 10 mg (8.8 %). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections was similar to placebo for mild, moderate and severe intensity reports. Urinary tract infection was reported more frequently in female patients treated with empagliflozin compared to placebo, but not in male patients.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

In clinical trials with empagliflozin plus linagliptin , genital infections in patients treated with empagliflozin / linagliptin(25 mg empagliflozin / 5 mg linagliptin: 3.0% ; 10 mg empagliflozin / 5 mg linagliptin :2.5%) were reported more frequently than for linagliptin but less freqeuntly than for empagliflozin. Overall, the frequencies for for Empagliflozin /linagliptin have been comparable to those reported from the empagliflozin clinical trials.

In empagliflozin trials, vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg (4.0 %) and empagliflozin 25 mg (3.9 %) compared to placebo (1.0 %). These infections were reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe in intensity.

Increased urination

In clinical trials with empagliflozin /linagliptin , increased urination in patients treated with for Empagliflozin plus linagliptin (25 mg empagliflozin / 5 mg linagliptin : 2.6 %;

10 mg Empagliflozin / 5 mg linagliptin : 1.4 %) was reported more frequently than for linagliptin and with similar frequency than for empagliflozin. Overall, the frequencies for empagliflozin /Linagliptin have been comparable to those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, increased urination (including the predefined terms pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin (empagliflozin 10 mg: 3.5 %, empagliflozin 25 mg: 3.3 %) compared to placebo (1.4 %). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin (< 1 %).

Volume depletion

In clinical trials, there was no notable difference in the frequency of volume depletion in patients treated with for Empagliflozin /linagliptin (for Empagliflozin /linagliptin 10 mg/5 mg: 0.8 %) compared to the patients treated with empagliflozin and linagliptin. The frequencies have been comparable to those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, the overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was similar in patients treated with empagliflozin (empagliflozin 10 mg: 0.6 %, empagliflozin 25 mg: 0.4 %) and placebo (0.3 %). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2.3 %) or empagliflozin 25 mg (4.3 %) compared to placebo (2.1 %).

Blood creatinine increased/Glomerular filtration rate decreased

In clinical trials with for Empagliflozin /linagliptin, the frequency of patients with increased blood creatinine (for Empagliflozin /linagliptin 10 mg/5 mg: 0%) and decreased glomerular filtration rate (for Empagliflozin /linagliptin 10 mg/5 mg: 0.6%) has been comparable to those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, the overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%).

Elderly

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In clinical trials, nineteen patients 75 years or older were treated with empagliflozin /Linagliptin. No patient was older than 85 years. The safety profile of empagliflozin /Linagliptin did not differ in the elderly. Based on empagliflozin experiences, elderly patients may be at increased risk of volume depletion (see sections 4.2, 4.4 and 5.2)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Talk to your doctor or you can report directly via The Egyptian Pharmacovigilance Center:

Address: 21 Abd El Aziz Al Soud Street, El-Manial, Cairo, Egypt, And PO Box: 11451

Telephone: (+2) 02 25354100, Extension: 1303

Fax: +202 – 23610497

Email: **PV.report@edaegypt.gov.eg**

Online reporting: http://www.epvc.gov.eg

Or Zeta pharma PV Email: pv@zeta-pharma.com

4.9 Overdose

Symptoms

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4 times the highest recommended daily dose) 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. There is no experience with doses above 800 mg in humans.

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were generally well tolerated. There is no experience with doses above 600 mg in humans.

Treatment

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required.

The removal of empagliflozin by haemodialysis has not been studied. Linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action

empagliflozin /Linagliptin combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, DPP-4 inhibitor.

Empagliflozin

Empagliflozin is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of SGLT2. Empagliflozin does not inhibit other glucose 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 hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes mellitus by reducing renal glucose re-absorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes mellitus and hyperglycaemia 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.

In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and was continuous over the 24-hour dosing

interval. Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78 g/day. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

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. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

Linagliptin

Linagliptin is an inhibitor of the enzyme DPP-4 an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide¬1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins 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. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000-fold selectivity versus DPP-8 or DPP-9 activity *in vitro*.

5.2 Pharmacokinetic properties

The rate and extent of absorption of empagliflozin and linagliptin in empagliflozin /Linagliptin are equivalent to the bioavailability of empagliflozin and linagliptin when administered as individual tablets.The pharmacokinetics of empagliflozin and linagliptin as single agents have been extensively characterized in healthy subjects and patients with type 2 diabetes. Pharmacokinetics were generally similar in healthy subjects and in patients with type 2 diabetes.

for Empagliflozin /linagliptin showed a similar food effect as the individual active substances. for Empagliflozin /linagliptin can therefore be taken with or without food.

Empagliflozin

Absorption

After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} 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 area under the concentration-time curve (AUC) and C_{max} were 1,870 nmol.h and 259 nmol/L with empagliflozin 10 mg and 4,740 nmol.h 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.

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 C_{max} 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 [^{14}C]-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 suggest 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 [^{14}C]-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.

Linagliptin

Absorption

After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

After once daily dosing of 5 mg linagliptin, steady-state plasma concentrations are reached by the third dose. Plasma AUC of linagliptin increased approximately 33 % following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6 % and 28.5 %, respectively). Due to the concentration dependent binding of linagliptin to DPP-4, the pharmacokinetics of linagliptin based on total exposure is not linear; indeed total plasma AUC of linagliptin increased in a less than dose-proportional manner while unbound AUC increases in a roughly dose-proportional manner.

The absolute bioavailability of linagliptin is approximately 30 %. Co-administration of a high-fat meal with linagliptin prolonged the time to reach C_{max} by 2 hours and lowered C_{max} by 15 % but no influence on AUC_{0-72h} was observed. No clinically relevant effect of C_{max} and T_{max} changes is expected; therefore linagliptin may be administered with or without food.

The steady state plasma AUC $_{\tau,ss}$ and $C_{max,ss}$ concentrations of linagliptin were 153 nmol*hr/L and 12.9 nmol/L for linagliptin 5 mg once daily for 7 days.

Distribution

As a result of tissue binding, the mean apparent volume of distribution at steady-state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1,110 litres, 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 75-89 % 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, 70-80 % of linagliptin was bound to other plasma proteins than DPP-4, hence 30-20 % were unbound in plasma.

Biotransformation

Following a [^{14}C] linagliptin oral 10 mg dose, approximately 5 % of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13.3 % of linagliptin at steady-state was detected which was found to be pharmacologically inactive and thus to not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Elimination

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours) that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the medicinal product. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours.

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

Renal impairment

Empagliflozin

In patients with mild, moderate or severe renal impairment (eGFR <30 to <90 mL/min/1.73 m^2) and patients with kidney failure or 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 (see section 4.2).

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Linagliptin

A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal insufficiency compared to subjects with normal renal function. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with ESRD on haemodialysis. In addition patients with T2DM and severe renal impairment (<30 mL/min) were compared to T2DM patients with normal renal function.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7-fold was observed compared with control. Exposure in T2DM patients with severe RI was increased by about 1.4-fold compared to T2DM patients with normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis (see section 4.2).

Hepatic impairment

Empagliflozin

In patients with mild, moderate and severe hepatic insufficiency (Child-Pugh classification), mean AUC and C_{max} of empagliflozin increased (AUC by 23 %, 47 %, 75 % and C_{max} by 4 %, 23 %,48 %) compared to subjects with normal hepatic function (see section 4.2).

Linagliptin

In non-diabetic patients with mild, moderate and severe hepatic insufficiency (according to the Child-Pugh classification), mean AUC and C_{max} of linagliptin were similar to healthy subjects following administration of multiple 5 mg doses of linagliptin.

Body mass index

No dosage adjustment is necessary for empagliflozin /Linagliptin based on body mass index. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin or linagliptin based on population pharmacokinetic analysis.

Gender

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

Race

No clinically relevant difference in pharmacokinetics of empagliflozin and linagliptin were seen in population pharmacokinetic analysis and dedicated phase I studies.

Elderly

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin or linagliptin based on population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric patients

Empagliflozin

A paediatric Phase I 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.

Linagliptin

A paediatric Phase 2 study examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin 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. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA_{1c} (-0.63% vs -0.48%, n.s.). Due to the limited nature of the data set the results should be interpreted cautiously.

Drug interactions

No drug interaction studies have been performed with empagliflozin /Linagliptin and other medicinal products; however, such studies have been conducted with the individual active substances.

In vitro assessment of empagliflozin

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.

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 Organic Anion Transporter 1 (OAT1) and Organic Cation Transporter 2 (OCT2). Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with medicinal products 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 C_{max} 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.

In vitro assessment of linagliptin

Linagliptin was a substrate for OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2, suggesting a possible OATP8-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and reabsorption of linagliptin *in vivo*. OATP2, OATP8, OCTN1, OCT1 and OATP2 activities were slightly to weakly inhibited by linagliptin.

6. Pharmaceutical particulars

6.1 List of excipients

Empacoza plus 10 mg/5 mg film-coated tablets

Tablet core

Mannitol 300DC

Starch 1500

Crospovidone xl

Magnesium stearate

Colloidal silicone dioxide (Aerosil 200)

Povidone K30

Film coating

Hydroxy propyl methyl cellulose E5

Talc purified

Titanium dioxide (CINo. 77891)

Polyethylene glycol 6000

Empacoza plus 25 mg/5 mg film-coated tablets

Tablet core

Mannitol DC

Pregelatinized Starch (starch 1500)

Crospovidone xl

Magnesium stearate

Colloidal silicone dioxide (Aerosil 200)

Povidone K30

Film coating

Hypromellose E15

Talc

Titanium dioxide (CINo. 77891)

Polyethylene glycol 6000

Ethanol 96% (evaporate)

Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store at temperature not exceeding 30 ° C in dry place .

6.5 Nature and contents of container

Carton box containing 1,2 or 3 AL/AL strips each of 10 film coated tablets + inner leaflet

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

Manufacturer :Atco pharma for pharmaceutical industries

license holder : pharmaglob

ايمباكوزا بلس 1
0 مجم /5 مجم & 25 مجم /5 مجم
(اقراص مغلفة)

▼هذا الدواء يخضع لمراقبة إضافية. والذى يسهل تحديد بطريقة سريعة معلومات السلامة. يمكنك المساعدة عن طريق الإبلاغ عن اي اثار جانبية قد تحصل عليها. انظر نهاية القسم 4 لكيفية الإبلاغ عن الآثار الجانبية

اقرأ هذه النشره بعنايه قبل البدء في استعمال هذا الدواء لأنها تحتوي علي معلومات هامة بالنسبة لك.

- احتفظ بهذه النشره , ربما قد تحتاج ان تقراها مره اخري
- اذا كان لديك المزيد من الاسئله , يرجاء ان تسال طبيبك او الصيدلي أو التمريض
- هذا الدواء موصوف لك خصيصاً , و لا ينبغي ان تعطي منه للاخرين , لانه قد يسبب لهم الاذي حتي اذا كانت اعراضهم مشابهه لاعراضك

اذا عانيت من اية اثار جانبية فاخبر الطبيب او الصيدلي وذلك يتضمن اية اثار جانبية محتملة غير مدرجة بهذه النشرة (انظر القسم 4)

ماذا تحتوى هذه النشرة

1. ما هو ايمباكوزا بلس و فيم يستخدم ؟

ما هو ايمباكوزا بلس

ايمباكوزا بلس دواء لعلاج مرض السكري و يحتوي علي المواد الفعالة " إيمباجليفلوزين" و"لیناجلیبتین".

• يعمل " إيمباجليفلوزين" عن طريق منع بروتين في الكليتين يسمي صوديم – جلوكوز مساعدات الناقلات 2(SGLT2) . يمنع SGLT2 الجلوكوز من أن يفرز في البول عن طريق إمتصاص الجلوكوز مرة أخري في مجري الدم حين يتم تصفية الدم في الكليتين. يمنع هذا البروتين ، يقوم الدواء بإزالة الجلوكوز (سكر الدم) ، الصوديم (الأملاح) و المياه عن طريق البول ، مما يساعد علي خفض مستويات الجلوكوز بالدم المرتفع بسبب داء السكري من النوع 2 .

• يعمل "لیناجلیبتین " بطريقة أخري ، عن طريق تمكين البنكرياس من إنتاج مزيد من الإنسولين لخفض مستويات السكر ، عن طريق منع بروتين يسمي DPP-4.

يتم إضافة ايمباكوزا بلس للمتفورمين مع / أو للسلفونيل يوريا لمعالجة مرض السكري النوع 2 للمرضي البالغين الذين لا يستطيعون التحكم بمرض داء السكري حين يتم علاجهم بالميتفورمين مع / أو بالسلفونيل يوريا بالإضافة إلي إيمباجليفلوزين ، حين يتم علاجهم بالميتفورمين مع / أو بالسلفونيل يوريا بالإضافة إلي لیناجلیبتین .

يمكن إستخدام ايمباكوزا بلس بديلا عن إيمباجليفلوزين و لیناجلیبتین في أقراص منفردة . في هذه الحالة ، لا تستمر في اخذ أي من هذه الأقراص منفردة في حالة تناولك ايمباكوزا بلس .
من المهم أن تحافظ علي نظامك الغذائي و ممارسة الرياضة كما أوصي الطبيب ، الصيدلي او التمريض

ما هو داء السكري من النوع 2؟

داء السكري النوع 2 هو المرض الذي يأتي من كلا من الجينات و نمط حياتك ، إذا كان عندك داء السكري النوع 2 ، البنكرياس لا يستطيع ان يصنع ما يكفي من الأنسولين للسيطرة علي مستوي الجلوكز في دمك، و جسمك غير قادر علي إستخدام الأنسولين الخاص به بشكل فعال مما يؤدي إلي إرتفاع مستوي السكر في الدم التي يمكن أن تؤدي إلي مشاكل طبيية مثل أمراض القلب و الكلي و العمي و ضعف الدورة الدموية في الأطراف .

2-ما يجب أن تعرفه قبل تناول ايمباكوزا بلس ؟

لا تأخذ ايمباكوزا بلس

-إذا كنت تعاني من حساسية تجاة إيمباجليفلوزين ، لیناجلیبتین ، أي مثبط SGLT2 أخر (مثل : داباجليفلوزين ، كاناجليفلوزين)، أي مثبط DPP-4 أخر (مثل : سيتاجليبتين ، فيلداجليبتين) ، أو أي من المكونات الأخري الموجودة من هذا الدواء (المدرج في القسم 6)
-إذا لديك او كان لديك سابقا بعض المشاكل في البنكرياس مثل إلتهاب بالبنكرياس أو جراحة في البنكرياس

المحاذير و الإحتياطات

تحدث الي طبيبك قبل أن تأخذ هذا الدواء و خلال العلاج :

- ما تستطيع فعله لمنع الجفاف
- إذا كان لديك داء السكري النوع 1 (لايستطيع جسمك إنتاج الأنسولين) . لا يجب أخذ ايمباكوزا بلس لمعالجة داء السكري النوع 1
- إذا عانيت فقدان سريع للوزن ، القيء أو الشعور بالغثيان ، ألم بالمعدة ، العطش الشديد ،التنفس السريع و العميق ، إرتباك ، شعور زائد بالنعس أو التعب ، رائحة حلوة لأنفاسك ، طعم حلو أو معدني في فمك ، أو رائحة مختلفة للبول أو العرق . تواصل مع طبيبك أو أقرب مستشفي علي الفور حيث أن هذا يمكن أن يكون من أعراض " الحماض الكيتوني السكري " مشكلة نادرة ولكنها خطيرة ومهددة للحياة في بعض الأحيان ، مشكلة يمكن أن تحدث مع داء السكري لإرتفاع مستويات الكيتونات في البول أو الدم . و تظهر في التحليل . زيادة المخاطرمن حدوث الحماض الكيتوني السكري يمكن أن يزداد بسبب ساعات الصيام الطويلة ، إستهلاك مفرط للكحول ، جفاف أو نقص مفاجئ في جرعة الأنسولين ، أو بعد جراحة كبري أو مرض خطير يؤدي إلي زيادة إحتياجك للإنسولين .
- إذا كنت تتناول أدوية أخري لمرض داء السكري المعروف ب "سلفونيل يوريا " (مثل : جليميبيرايد ، جليبيزايد) مع / أو الأنسولين . قد يرغب طبيبك في تقليل جرعتك من هذه الادوية حين يتم تناولهم جميعا مع ايمباكوزا بلس ، لتجنب الإنخفاض الشديد للسكر في الدم .
- إذا عانيت أو مازلت تعاني من مرض بالبنكرياس .
- إذا كان لديك مشاكل خطيرة بالكلي . قد ينصحك طبيبك بأخذ دواء أخر .

كما هو متعارف عليه يجب علي مرضي داء السكري التحقق من القدمين بإنتظام و الإستماع لنصائح أخري من قبل أخصائي الرعاية الصحية الخاص بك فيما يخص العناية بالقدمين .

وظائف الكلي

قبل بدء العلاج بتناول ايمباكوزا بلس و بشكل منظم خلال العلاج ، سنتحقق طبيبك من مدي كفاءة الكليتين.

سكر البول

بسبب طريقة عمل هذا الدواء ، ستكون نتائج تحليل سكر البول إجابية أثناء تناول هذا الدواء .

الأطفال والمراهقين

لم يتم دراسة ايمباكوزا بلس في الأطفال والمراهقين ، لذلك لا يوصى باستخدامه في الأطفال والمراهقين الذين تتراوح أعمارهم بين 18 عاما أو أقل.

الادوية الاخري و ايمباكوزا بلس

أخبر طبيبك أو الصيدلي إذا كنت تتناول ، تناولت مؤخرا أو قد تتناول أي أدوية أخرى.
وعلي وجه الخصوص يجب عليك أن تخبر طبيبك إذا كنت تستخدم الأدوية التالية.

- أدوية أخري لعلاج مرض داء السكري، مثل الأنسولين أو سلفونيل يوريا . في هذه الحالة قد يرغب طبيبك في خفض جرعات هذه الأدوية الأخري لتجنب الإنخفاض الشديد للسكر بالدم .
- إذا كنت تتناول دواء يستخدم لإزالة الماء من الجسم (مدر للبول) ، قد يطلب منك الطبيب التوقف عن تناول ايمباكوزا بلس .
- الأدوية التي قد تؤثر علي تكسين إيمباجليفلوزين ، ليناجليبتين في الجسم ، مثل ريفامبيسين (مضاد حيوي يستخدم لمرض السل) أو بعض الأدوية المستخدمة في علاج نوبات الصرع (مثل كاربامازبين، فينوباربيتال أو فينيتوين) . يمكن أن تقل فاعلية ايمباكوزا بلس

الحمل والرضاعة

إذا كنت حاملا أو تعتقدين أنك حامل أو تخططين لإنجاب طفل أستشيري طبيبك قبل تناول هذا الدواء من غير معروف ما إذا كان هذا الدواء ضار بالجنين . كتدبير وقائي من الأفضل تجنب إستخدام هذا الدواء خلال فترة الحمل .
لا تستخدم هذا الدواء اثناء الرضاعة حيث إنه غير معروف إذا كان تمر المواد الفعالة من حليب الثدي أم لا . من غير المعروف ما إذا كان ايمباكوزا بلس له تأثير علي الخصوبة في البشر

القيادة واستخدام الآلات

ايمباكوزا بلس له تأثير بسيط علي القدرة علي القيادة و إستخدام الآلات .
تناول هذا الدواء بالإضافة إلي سلفونيل يوريا أو الأنسولين يمكن أن يؤدي إلي إنخفاض شديد في مستوي السكر بالدم ، و هذا قد يؤدي لأعراض مثل الإهتزاز ، التعرق و تغير في الرؤية ، مما يؤثر علي قدرتك علي القيادة أو إستخدام الآلات . لا تقود أو تستخدم أدوات أو الآلات إذا شعرت بهذه الأعراض بينما تتناول ايمباكوزا بلس .

3- كيف تتناول ايمباكوزا بلس ؟

دائما تناول هذا الدواء كما وصف لك طبيبك .تحقق من طبيبك أو الصيدلي ما لم تكن متأكد .

- إذا كان كان سنك 75 سنة أو أكثر حيث أن زيادة مرور البول يمكن أن يؤثر في توازن السوائل في الجسم و زيادة المخاطرة لحدوث جفاف . لمعرفة العلامات المحتملة للجفاف ، أنظر للقسم 4
- لا ينصح بتناول هذا الدواء إذا كان عمرك 75 أو أكثر .

تواصل مع طبيبك إذا تعرضت لأي من الآتي خلال تناولك ايمباكوزا بلس .

- إذا شعرت بأعراض إلتهاب البنكرياس الحاد مثل ألم مستمر و حاد بالبطن . الأعراض المحتملة موضحة في القسم 4 "الأعراض الجانبية المحتملة " قد يحتاج طبيبك لتغير علاجك .
- إذا أصبت بالقيئ، أسهال أو حمي ، أو لا تستطيع الأكل أو الشرب . من الممكن أن تؤدي هذه الحالات للجفاف . و قد يطلب منك طبيبك التوقف عن تناول ايمباكوزا بلس حتي تتعافي ، لتجنب خسارة سوائل من الجسم كبيرة .
- إذا كان لديك عدوي خطيرة بالكلي أو بالمجري البولي مع حرارة . و قد يطلب منك طبيبك التوقف عن تناول ايمباكوزا بلس حتي تتعافي .
- إذا واجهت تقرحات جلدية قد تكون علامة من حالة تسمي الفقعان الفقاعي . و قد يطلب منك طبيبك التوقف عن تناول ايمباكوزا بلس

تحدث إلي طبيبك علي الفور إذا أصبت بمزيج من الأعراض التالية ،ألم ،ألم بالضغط ، إحمرار أو إنتفاخ في الأعضاء التناسلية أو في المنطقة فيما بين الاعضاء التناسلية و فتحة الشرج مع حمي أو الشعور عموما بتوعك . هذه الأعراض يمكن أن تكون علامة لعدوة نادرة أو خطيرة أو مهددة بالحياة تسمي إلتهاب اللفافة النخري أو غنغرينة فورنير التي تقوم بتدمير الخلايا تحت الجلد . يجب معالجة غنغرينة فورنير علي الفور.

ما هي أهم المعلومات التي يجب أن أعرفها عن ايمباكوزا بلس ؟

عدوى الخميرة المهبلية: النساء اللواتي يأخذن ايمباكوزا بلس قد يصبن بالخميرة المهبلية
أعراض عدوي الخميرة المهبلية تشمل:
الالتهابات رائحة مهبلية . إفرازات مهبلية بيضاء أو مصفرة (قد تكون الإفرازات متكتلة أو تبدو وكأنها الجبن) الحكة المهبلية

عدوى الخميرة في القضيب (التهاب الحشفة أو التهاب الأمعاء)
الرجال الذين يأخذون ايمباكوزا بلس قد تحصل علي عدوى الخميرة من الجلد حول القضيب
قد يحدث لبعض الرجال الذين لم يتم ختانهم تورم القضيب الذي يجعل من
من الصعب سحب الجلد حول طرف القضيب. أعراض أخرى من الخميرة
:وتشمل عدوى القضيب
أو الحكة أو تورم القضيب , طفح القضيب ||
رائحة كريهة من القضيب . الألم في الجلد حول القضيب التحدث إلي طبيبك حول ما يجب القيام به إذا كنت مصاب بأعراض عدوى الخميرة من
المهبل أو القضيب
قد يقترح عليك طبيبك استخدام دواء مضاد للفطريات دون وصفة طبية. تحدث إلي
طبيبك علي الفور إذا كنت تستخدم دواء مضاد للفطريات دون وصفة طبية و
الأعراض الخاصة بك لا تزول.

العناية بالقدمين

ما عليك فعله إذا نسيت تناول القرص يعتمد علي الوقت المتبقي حتي الجرعة التالية .

- إذا كان من 12 ساعة أو أكثر حتي الجرعة التالية ، فتناول ايمباكوزا بلس حالما تتذكر . ثم تناول الجرعة التالية في موعدها المعتاد.
- إذا كانت أقل من 12 ساعة حتي الجرعة التالية ، تخطي الجرعة المنسية ، ثم تناول الجرعة التالية في موعدها المعتاد .
- لا تتناول ضعف الجرعة من هذا الدواء لتعويض الجرعة المنسية .

إذا توقفت عن تناول ايمباكوزا بلس

لا تتوقف عن تناول هذا الدواء دون إستشارة طبيبك أولا . قد تزيد مستويات السكر في دمك حين تتوقف عن تناول ايمباكوزا بلس

إذا كان لديك المزيد من الأسئلة عن إستخدام هذا الدواء اسأل طبيبك ، الصيدلي أو التمريض .

٤- الآثار الجانبية المحتملة

مثل جميع الأدوية يمكن أن يسبب هذا الدواء آثار جانبية ، علي الرغم من أن الجميع لا يحث معهم .

تواصل مع طبيبك أو أقرب مستشفي في الحال إذا عانيت من أي من الآثار الجانبية الخطيرة الآتيه :

- يحدث نادرا (قد يؤثر في 1 من 1,000 شخص)الحماض الكيتوني السكري(ارتفاع في مستويات الأجسام الكيتونية في الدم أو البول) . الحماض الكيتوني السكري حدث في المرضي الذين يعانون من مرض السكر النوع 1 و 2 و قت علاجهم بايمباكوزا بلس . الحماض الكيتوني السكري هي حالة خطيرة والتي تحتاج إلي المعالجة بالمستشفي . قد يؤدي الحماض الكيتوني السكري إلي الوفاة . قد يحدث الحماض الكيتوني السكري و إن كان مستوي السكر أقل من 250 مجم/ ديسيلتر . توقف عن أخذ ايمباكوزا بلس و أتصل بطبيبك في الحال إذا شعرت بالأعراض التالية:

- غثيان
- التعب أو نعاس غير عادي
- القيء أو الشعور بالغثيان
- صعوبة بالتنفس
- ألم بالمعدة أو بمنطقة البطن
- فقدان سريع في الوزن
- العطش الشديد
- عمق و سرعة في التنفس
- الإرتباك
- رائحة حلوة لأنفاسك ، طعم حلو أو معدني في فمك ، أو رائحة مختلفة للعرق أو البول

في حالة حدوث هذه الأعراض أثناء العلاج بإمباكوزا بلس ، تحقق من مستوي الكيتون في البول إذا كان ممكنا ،حتي و إن كان مستوي السكر في الدم أقل من 250 مجم / ديسيليتر .

تواصل مع طبيبك علي الفور إذا ما لاحظت أي من الأعراض الجانبية الآتية :

ردود فعل تحسسية ، نادرا ما يحدث (قد يؤثر علي 1 من 100 شخص) :

كم يجب أن تأخذ

الجرعة المبدائية هي 10 مجم إيمباجليفلوزين و 5 مجم لينا جليبتين مرة واحدة في اليوم . لهذه الجرعة فإنه متوفر ايمباكوزا بلس 10 مجم / 5 مجم أقراص مغلفة.

سيقرر طبيبك ما إذا كنت تحتاج لزيادة الجرعة إلي25 مجم إيمباجليفلوزين و 5 مجم لينا جليبتين مرة واحدة في اليوم

إذا كنت تأخذ 25 مجم إيمباجليفلوزين و 5 مجم لينا جليبتين في هيئة أقراص منفردتو بدأت بتناول إيمباجليفلوزين/ لينا جليبتين ، فيمكنك أن تبداء بأخذ 25 مجم إيمباجليفلوزين و 5 مجم لينا جليبتين مباشرة

الفشل الكلوي

تحدث إلي طبيبك إذا كان لديك مشاكل في الكلي . قد يحد طبيبك من جرعتك أو يقرر إستخدام دواء بديل .

فشل كبدي

تحدث إلي طبيبك إذا كان لديك فشل كلوي حاد . لا ينصح بتناول ايمباكوزا بلس و قد يقرر طبيبك إستخدام دواء بديل .

كبار السن

لا توجد دراسات كافية علي المرضي من سن 75 أو أكثر . لا يجب بدء تناول ايمباكوزا بلس للمرضي الذين تتخطي أعمارهم 75 سنة .

كيفية تناول هذا الدواء

يتم إبتلاع القرص كاملا مع المياه .
يمكن تناول ايمباكوزا بلس مع أو بدون طعام .
يمكن تناول القرص في أي وقت من اليوم ، و مع ذلك حاول أن تأخذه في نفس الوقت يوميا .هذا سيساعدك علي تذكر تناوله .
قد يصف لك طبيبك أدوية أخري لعلاج داء السكري بالتزامن مع ايمباكوزا بلس ، تذكر دائما بإستخدام كل الأدوية حسب تعليمات الطبيب للحصل علي أفضل النتائج

النظام الغذائي و ممارسة الرياضة يمكن أن يساعد الجسم علي إستخدام أفضل لسكر الدم . من المهم المحافظة علي النظام الغذائي و برنامج ممارسة الرياضة كما هو موصي من قبل الطبيب مع تناول هذا الدواء .

إذا تناولت ايمباكوزا بلس أكثر مما ينبغي

إذا تجاوزت الكمية المحددة من هذا الدواء أكثر مما ينبغي ، عليك التحدث إلي طبيبك أو الذهاب للمستشفي في الحال . و قم بأخذ الدواء معك .

في حالة نسيان تناول ايمباكوزا بلس

- حكة
- طفح جلدي
- زيادة في أنزيم الدم أميليز
- زيادة في أنزيم البنكرياس ليباز
- الشعور بالعطش

غير شائع

- صعوبة أو ألم عند تفريغ المثانة
- قد تظهر تحليل الدم تغيرات في مستويات الدهون في الدم ، زيادة في كمية كرات الدم الحمراء (زيادة في حجم الخلايا المكتسة)، تغيرات في وظائف الكلي (انخفاض معدل التصفية و زيادة في الكيرياتنين بالدم)

نادرا ما يحدث

- قرح في الفم .

معدل حدوثه غير معرف (لا يمكن تقديره من البيانات الموجودة)

- تقرحات بالجلد (الفقمان الفقاعي).
- إلتهاب اللفافة في النخري أو غنغرينة فورنير و هي عدوي خطيرة في الأنسجة الرخوة في الأعضاء التناسلية أو في المنطقة ما بين الأعضاء التناسلية و الشرج.
- ألم في المفاصل

للإبلاغ عن الآثار الجانبية

- إذا كنت تعاني من أي آثار جانبية يجب الإبلاغ عنها إلى طبيبك أو الصيدلي، هذا يشمل أي اثار جانبية محتملة حتى لو لم تكن مدرجة في هذه النشرة.

يمكنك أيضا الإبلاغ عن الآثار الجانبية مباشرة عن طريق البريد الألكتروني:

Egyptian Pharmaceutical Vigilance Center
E-mail:
PV.report@edaegypt.gov.eg
Zeta Pharma for pharmaceutical industries
E-mail: PV@zeta-pharma.com

بإبلاغك عن الأعراض الجانبية فإنك تساعد علي توفير المزيد من المعلومات عن سلامة هذا الدواء .

5- كيفية تخزين ايمباكوزا بلس

يحفظ بعيداً عن متناول الأطفال

لا تستخدم هذا الدواء بعد تاريخ انتهاء الصلاحية المذكورة على الشريط و العبوة بعد تاريخ انتهاء الصلاحية

قد يتسبب هذا الدواء بردود فعل تحسسية و التي يمكن أن تكون خطيرة ، بما في ذلك شري (ارتيكاريا) و إنتفاخ في الوجه ، الشفتين ،اللسان و الحلق مما قد يؤدي إلي صعوبة في التنفس و البلع (وذمة وعائية)

<u>التهاب بالبنكرياس (غير شائع الحدوث):</u>

قد يسبب هذا الدواء التهاب بالبنكرياس ، و الذي يظهر في هيئة ألم مستمر و شديد بالبطن (المعدة) الذي قد يمتد إلي ظهرك ، و غالبا يكون مصاحبا بالقيء أو الشعور بالغثيان . سيحتاج طبيبك إلي تغير علاجك

إنخفاض السكر بالدم ، شائع الحدوث (قد يؤثر علي 1 من 10 أشخاص):

إذا كنت تتناول ايمباكوزا بلس مع أدوية أخري التي قد تؤدي إلي خفض مستوي سكر ، مثل سلفونيل يوريا أو الأنسولين ، أنت في خطر الإصابة بإنخفاض شديد لسكر الدم . أعراض الإنخفاض الشديد في سكر الدم قد تتضمن :

- إهتزاز ، تعرق ، الشعور بالقلق الشديد أو الإرتباك ، ضربات قلب سريعة
- شعور شديد بالجوع ، صداع

سيخبرك طبيبك كيف تعالج سكر الدم المنخفض و ماذا تفعل إذا تعرضت لأي من الأعراض أعلاه . إذا كان لديك أحد أعراض انخفاض السكر في الدم ، تناول أقراص جلوكوز ، وجبة خفيفة غنية بالسكر أو اشرب عصير فاكهة . قم بقياس مستوي السكر بالدم إذا أمكن و أسترح.

<u>عدوي المسالك البولية ، يحدث عادة</u>

علامات عدوي المسالك البولية هي :

- أحساس بالحرقان عند التبول
- البول الذي يظهر غائم
- ألم في الحوض ، أو وسط الظهر (حين تصلب الكلي بالعدوي)

قد تكون الرغبة الملحة للتبول أو تكرار التبول بسبب طريقة عمل الدواء . و لكن من الممكن أن يكونوا من علامات عدوي المسالك البولية، إذا لحظت زيادة في هذه الأعراض ، يجب عليك التواصل مع طبيبك .

<u>فقدان سوائل الجسم (الجفاف) غير شائع الحدوث</u>

هذه العلامات غير محددة ، و لكنها قد تتضمن :

- شعور غير معتاد بالعطش
- دوار أو دوخة حين الوقوف
- إغماء أو فقدان الوعي

أعراض جانبية أخري حين تناول ايمباكوزا بلس شائعة

- العدوي الفطرية بالأعضاء التناسلية (المهبل أو القضيب) مثل القلاع
- التهاب الأنف و الحلق
- سعال
- مرور المزيد من البول أو الحاجة إلي التبول كثير من الأحيان

لا تستخدم هذا الدواء إذا لاحظت أي ضرر أو علامات للعبث على عبوة الدواء

يحفظ في درجه حراره لا تزيد عن 30درجه مئويه في مكان جاف.
مدة الصلاحية : عامان

لا تتخلص من أي أدوية عن طريق مياه الصرف الصحي أو النفايات المنزلية. اسأل الصيدلي عن كيفية التخلص ، هذه الخطوات ستساعدك علي المحافظة علي البيئة

6- مكونات العبوة و معلومات أخري

علي ماذا يحتوي ايمباكوزا بلس
ايمباكوزا بلس 5/10 : يحتوي كل قرص مغلف علي
المواد الفعالة :
10 مجم ايمباجليفلوزين و 5 مجم لیناجلیبتین
مواد أخري :
مانيتول DC 300 ، نشا1500 ، كروسبوفيدونxl ،بوفيدونk30 ، ثاني أكسيد الغروي(ايروسيل 200) ، سترات الماغنسيوم
مواد التغليف :
هيدروكسي بروبيل مثيل سيليلوز E5 ، ثاني اوكسيد تيتانيوم ، تلك نقي ، بولي إثيلين جليكول 6000
ايمباكوزا بلس 5/25 : يحتوي كل قرص مغلف علي
المواد الفعالة :
25 مجم ايمباجليفلوزين و 5 مجم لیناجلیبتین
مواد أخري :
مانيتول DC ، جيلاتين النشا(نشا1500) ، كروسبوفيدونxl ،بوفيدونk30 ، ثاني أكسيد الغروي(ايروسيل 200) ، سترات الماغنسيوم
مواد التغليف :
هيروملوز E15، ثاني اوكسيد تيتانيوم ، تلك ، بولي إثيلين جليكول 6000، ماء نقي ، ايثانول 96% (يتبخر)

العبوة :
علبة كرتون تحتوي علي 1 أو 2 أو 3 (AL /AL) شرائط ، كل شريط يحتوي علي 10 أقراص مغلفة + نشرة داخلية
المصنع شركة اتكوفارما للصناعات الدوائية
صاحب الرخصة : شركة فارماجلوب