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

GLUCRETA LM

WARNING: LACTIC ACIDOSIS

Lactic acidosis caused by metformin accumulation (plasma concentration >5 mcg/mL) is a rare but potentially severe consequence; if it occurs, mortality is ~50%

Risk increases with certain conditions (eg, renal impairment, sepsis, dehydration, excess alcohol intake, and hepatic impairment); concomitant use of certain drugs (eg, carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (eg, acute congestive heart failure)

Onset is subtle, accompanied only by nonspecific symptoms (eg, malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress)

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate

If lactic acidosis is suspected, discontinue drug and immediately hospitalize the patient

Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30-60 mL/minute/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinate contrast; reevaluate eGFR 48 hr after imaging procedure; restart therapy if renal function stable

1. Generic Name

Linagliptin, Dapagliflozin and Metformin Hydrochloride (SR) Tablets.

2. Qualitative and quantitative composition

GLUCRETA LM 5/10/500

Each film coated bilayer tablet contains:

Linagliptin……..…5 mg

Dapagliflozin Propanediol U.S.P.

eq. to Dapagliflozin……....10 mg

Metformin Hydrochloride I.P……...500 mg

(as sustained release form)

Excipients…….q.s.

Colours: Yellow Oxide of Iron Lake & Titanium Dioxide I.P.

GLUCRETA LM 5/10/1000

Each film coated bilayer tablet contains:

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Dapagliflozin Propanediol U.S.P.

eq. to Dapagliflozin……....10 mg

Metformin Hydrochloride I.P……..1000 mg

(as sustained release form)

Excipients……..….q.s.

Colours: Yellow Oxide of Iron Lake & Titanium Dioxide I.P.

3. Dosage form and strength

Dosage form: Film coated bilayer Tablets

Strength: Linagliptin 5 mg, Dapagliflozin Propanediol 10 mg, Metformin Hydrochloride 500 mg/1000 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of in patients with Type 2 Diabetes Mellitus inadequately controlled on Metformin alone.

4.2 Posology and method of administration

Posology

The recommended starting dose is one Glucreta LM tablet once daily.

Always take this medicine exactly as your doctor or pharmacist has told you.

Check with your doctor or pharmacist if you are not sure. Glucreta LM tablet are for oral use. You should swallow your Tablets whole with a drink of water.

Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys.

Method of administration

Oral use

Tablet should be swallowed whole & not to be chewed or crushed.

4.3 Contraindications

Hypersensitivity to any ingredient of the composition.

4.4 Special warnings and precautions for use

Metformin

Metformin associated with a decrease to subnormal levels of previously normal serum vitamin B-12 levels, without clinical manifestations; measure hematological parameters annually and vitamin B12 at 2- to 3-year intervals and manage any abnormalities

Lactic acidosis

Postmarketing cases of metformin-associated lactic acidosis, including fatal cases, reported Lactic acidosis has a subtle onset and may be accompanied by nonspecific symptoms (eg, malaise, myalgias, abdominal pain, respiratory distress, increased somnolence); however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis Metformin-associated lactic acidosis characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and increased lactate: pyruvate

ratio; metformin plasma levels generally >5 mcg/mL

Metformin decreases liver uptake of lactate increasing lactate blood levels, which may increase risk of lactic acidosis, especially in patients at risk If lactic acidosis suspected, institute general supportive measures promptly in a hospital setting, along with immediate discontinuation metformin-containing product Prompt hemodialysis recommended for diagnosis or strong suspicion of lactic acidosis to correct acidosis and remove accumulated metformin; hemodialysis often results in symptom reversal and recovery.

Lactic acid risk factors and management

Renal impairment: Obtain eGFR before initiating, contraindicated if eGFR <30 mL/min/1.73 m2; obtain eGFR at least annually, and more often for patients at higher risk (eg, elderly)

Drug interactions: Coadministration with certain drugs may increase risk, such as those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation (eg, cationic drugs)

Aged ≥65 years greater likelihood of hepatic, renal, or cardiac impairment compared with younger patients; assess renal function more frequently

Radiological studies with iodinated contrast: May cause acute decrease in renal function and occurrence of lactic acidosis; discontinue metformin-containing products at time of, or prior to, iodinated contrast imaging procedure in patients with history of hepatic impairment, alcoholism, heart failure, or if administered intra-arterial iodinated contrast; reevaluate eGFR 48 hr after procedure, and restart metformin-containing drug if renal function stable

Surgery/procedures: Withholding food and fluids during surgical or other procedures may increase risk for volume depletion, hypotension, and renal impairment; temporarily discontinue metformin-containing product while food and fluid intake is restricted

Hypoxic states: Metformin-associated lactic acidosis reported with acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia); cardiovascular collapse, acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia; if such events occur, discontinue metformin-containing product

Excessive alcohol intake: Alcohol potentiates effect of metformin on lactate metabolism and may increase risk of lactic acidosis

Hepatic impairment: Risk of lactic acidosis increased; this may be due to impaired lactate clearance resulting in higher lactate blood levels; avoid metformin-containing products with clinical or laboratory evidence of hepatic disease

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin secretagogues and insulin are known to cause hypoglycemia. The use linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in reported study. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with Linagliptin And Metformin Hydrochloride.

Linagliptin

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue Linagliptin And Metformin Hydrochloride, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Linagliptin And Metformin Hydrochloride.

Vitamin B Deficiency

In metformin, reported study of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B absorption from the B -intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B supplementation. Certain individuals (those with inadequate vitamin B or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B levels. Measure hematologic parameters on an annual basis and vitamin B at 2 to 3 year intervals in patients on Linagliptin And Metformin Hydrochlorideand manage any abnormalities.

Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the reported clinical trial and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Glucreta LM. If bullous pemphigoid is suspected, Linagliptin And Metformin Hydrochlorideshould be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

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. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits Linagliptin Dapagliflozin and Metformin Hydrochloride prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart

failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation Linagliptin And Metformin Hydrochloride.

Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In reported clinical trial, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in reported clinical trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Glucreta LM and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Linagliptin and Metformin Hydrochloride.

Dapagliflozin

Hypoglycemia

Dapagliflozin increases risk of urinary tract infections (UTIs), including life-threatening urosepsis and pyelonephritis that started as UTIs; evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Dapagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue; a lower dose of insulin or insulin secretagogue may be required Dapagliflozin increases risk for genital mycotic infections.

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (eg, sulfonylureas, insulin) or ethanol.

4.5 Drugs interactions

The serum concentration of Linagliptin can be increased when it is combined with Abametapir. The metabolism of Linagliptin can be increased when combined with Abatacept. Aminosalicylic acid may increase the hypoglycemic activities of Dapagliflozin. The metabolism of Dapagliflozin can be decreased when combined with Amiodarone.

The risk or severity of lactic acidosis can be increased when Acetazolamide is combined with Metformin.

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

Pregnancy and Lactation

<u>Pregnancy</u>

Based on animal data showing adverse renal effects, not recommended during the second and third trimesters of pregnancy.

Limited data in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage

Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk

There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy

Discuss potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women

Poorly controlled diabetes in pregnancy increases maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications; poorly controlled diabetes increases fetal risk for major birth defects, stillbirth, and macrosomia related morbidity

Animal data

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose

Lactation

There is no information regarding the presence in human milk, the effects on the breastfed infant, or the effects on milk production

Limited published studies report that metformin is present in human milk

However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production

Dapagliflozin is present in the milk of lactating rats

Because of the potential for serious adverse reactions in breastfed infants, advise women that use is not recommended while breastfeeding

Reproductive potential

Discuss potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women*Linagliptin*

No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943-times (rats) and 1943-times (rabbits) the 5 mg clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49-times the 5 mg clinical dose, based on exposure. Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

Metformin Hydrochloride

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2 and 6-times a clinical dose of 2000

mg, based on body surface area (mg/m) for rats and rabbits, respectively.

Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

Pediatric Use

Safety and effectiveness Linagliptin And Metformin Hydrochloridehave not been established in pediatric patients.

Geriatric Use

Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney

Linagliptin

In the 15 type 2 diabetes studies with linagliptin, 1085 linagliptin-treated patients were 65 years of age and older (including 131 linagliptin-treated patients 75 years of age and older). Of these 15 studies, 12 were double-blind placebo-controlled. In these 12 studies, 591 linagliptin-treated patients were 65 years of age and older (including 82 linagliptin-treated patients 75 years of age and older). In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

Metformin

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.

Renal Impairment

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. GLUCRETA LM is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m.

If GLUCRETA LM is discontinued due to evidence of renal impairment, linagliptin may be continued as a single entity tablet at the same total daily dose of 5 mg. No dose adjustment of linagliptin is recommended in patients with renal impairment. In the linagliptin treatment arm of the reported trial (63%) patients had renal impairment (eGFR <60 mL/min/1.73m). Approximately 20% of the population had eGFR ≥45 to <60 mL/min/1.73 m, 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m and 15% had eGFR <30 mL/min/1.73 m . The overall incidence of adverse reactions were generally similar between the linagliptin and placebo treatment arms.

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis Linagliptin Dapagliflozin and Metformin Hydrochloride is not recommended in patients with hepatic impairment.

4.7 Effects on ability to drive and use machines

Linagliptin Dapagliflozin and Metformin Hydrochloride has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia when Glucreta LM tablets is used in combination with other anti-diabetic medicinal products known to cause hypoglycaemia (e.g. sulphonylureas).

4.8 Undesirable effects

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Excessive thirst and urination.
- Lactic Acidosis [see Warnings and Precautions (4.3)]
- Pancreatitis [see Warnings and Precautions (4.3)]
- Use with Medications Known to Cause Hypoglycemia [see Warnings and Precautions (4.3)]
- Hypersensitivity Reactions [see Warnings and Precautions (4.3)]
- Vitamin B Deficiency [see Warnings and Precautions (4.3)]
- Severe and Disabling Arthralgia [see Warnings and Precautions (4.3)]
- Bullous Pemphigoid [see Warnings and Precautions (4.3)]

4.9 Overdose

In the event of an overdose with Linagliptin, Dapagliflozin and Metformin Hydrochloride 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 metformin from patients in whom Linagliptin And Metformin Hydrochloride overdosage is suspected.

Metformin

Overdose of metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin.

5. Pharmacological properties

5.1 Mechanism of Action

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.

Dapagliflozin:

Dapagliflozin is an orally active, highly selective SGLT2 inhibitor that improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption leading to urinary glucose excretion (glucuresis).

Metformin:

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.2 Pharmacodynamic properties

Linagliptin

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

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

Metformin

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

5.3 Pharmacokinetic properties

Linagliptin:

Absorption

Oral bioavailability of linagliptin is 30%.

Distribution

A single intravenous dose of 5mg results in a volume of distribution of 1110L. However an intravenous infusion of 0.5-10mg results in a volume of distribution of 380-1540L.

Metabolism:

An oral dose of linagliptin is excreted primarily in the feces. 90% of an oral dose is excreted unchanged in the urine and feces. The predominant metabolite in the plasma is CD1790 and the predominant metabolite recovered after excretion was M489(1). Other metabolites are produced through oxidation, oxidative degradation, N-acetylation, glucuronidation, and cysteine adduct formation. Other metabolites have been identified through mass spectrometry though no structures were determined. Metabolism of linagliptin is mediated by cytochrome P450 3A4, aldo-keto reductases, and carbonyl reductases.

Elimination

84.7% of linagliptin is eliminated in the feces and 5.4% is eliminated in the urine.

Dapagliflozin:

***Absorption*:** Oral dapagliflozin reaches a maximum concentration within 1 hour of administration when patients have been fasting. When patients have consumed a high fat meal, the time to maximum concentration increases to 2 hours and the maximum concentration decreases by half though a dose adjustment is not necessary. Oral dapagliflozin is 78% bioavailable.

Distribution:

118L.

Metabolism:

Dapagliflozin is primarily glucuronidated to become the inactive 3-O-glucuronide metabolite(60.7%). Dapagliflozin also produces another minor glucuronidated metabolite (5.4%), a de-ethylated metabolite (<5%), and a hydroxylated metabolite (<5%). Metabolism of dapagliflozin is mediated by cytochrome p-450(CYP) 1A1, CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP3A4, uridine diphosphate glucuronyltransferase (UGT)1A9, UGT2B4, and UGT2B7. Glucuronidation to the major metabolite is mediated by UGT1A9.

Excretion: 75.2% of dapagliflozin is recovered in the urine with 1.6% of the dose unchanged by metabolism. 21% of the dose is excreted in the feces with 15% of the dose unchanged by metabolism.

Metformin:

Absorption

The intestinal absorption of metformin may be primarily mediated by plasma membrane monoamine transporter (PMAT, encoded by gene *SLC29A4*), which is expressed on the luminal side of enterocytes. However, there are currently no in-vivo data on the role of PMAT in the disposition and pharmacological effect of metformin. OCT3 (gene *SLC22A3*) is also expressed on the brush border of the enterocytes and may contribute to metformin uptake. In addition, OCT1 (gene *SLC22A1*), which is expressed on the basolateral membrane and cytoplasm of the enterocytes, may facilitate the transfer of metformin into the interstitial fluid. The role of OCT1 and OCT3 in the intestinal transport of metformin remains to be defined.

Distribution

The drug is widely distributed into body tissues including the intestine, liver, and kidney by organic cation transporters. There is a large interindividual variability in metformin pharmacokinetics as measured by differences in trough steady-state metformin plasma concentration ranging from 54 to 4133 ng/ml

Elimination

Metformin is not metabolized and is excreted unchanged in the urine, with a half-life of ~5 h. The population mean for renal clearance (CLr) is 510±120 ml/min. Active tubular secretion in the kidney is the principal route of metformin elimination.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of linagliptin dapagliflozin and metformin HCl.

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).

Metformin Hydrochloride

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses of up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and in vivo mouse micronucleus tests were negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

Dapagliflozin

In reported non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Reproductive and developmental toxicity

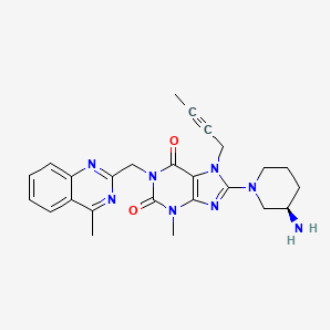
Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a reported juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

7. Description

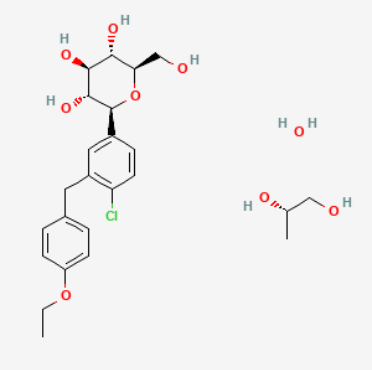
Linagliptin:

Linagliptin is 8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-ynyl-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]purine-2,6-dione. The Empirical formula is $C_{25}H_{28}N_8O_2$ and its molecular weight is 472.5 g/mol. The structural formula is:



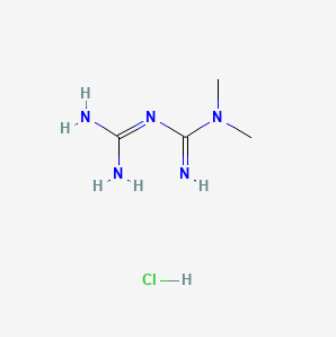
Dapagliflozin propanediol:

Dapagliflozin Propanediol is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol;(2S)-propane-1,2-diol;hydrate. The Empirical formula is $C_{24}H_{35}ClO_9$ and its molecular weight is 503.0 g/mol. The structural formula is:



Metformin Hydrochloride:

Metformin Hydrochloride is 1,1- dimethylbiguanide hydrochloride. The Empirical formula is $C_4H_{11}N_5$, HCL and its molecular weight is 165.6 g/mol. The structural formula is:



GLUCRETA LM 5/10/500

The Excipients used are Hydroxy propyl methyl Cellulose, Carboxy Methyl Cellulose, Poly vinyl Polypyrrolidine, Isopropyl Alcohol, Microcrystalline Cellulose, Crospovidone, Sodium Starch Glycolate, Purified Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxypopylmethyl Cellulose, Polyethylene glycol, Titanium Dioxide, Yellow Oxide of iron, Dichloromethane

GLUCRETA LM 5/10/1000

The Excipient used are Hydroxy propyl methyl Cellulose, Poly vinyl Polypyrrolidone, Microcrystalline Cellulose, Crospovidone, Sodium Starch Glycolate, Purified Talcum, Colloidal Silicon Dioxide, Magnesium Stearate, Titanium Dioxide, Yellow Oxide of Iron, Purified Talcum, Isopropyl Alcohol, Dichloromethane

8. Pharmaceutical particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

GLUCRETA LM is available in pack of 10 Tablet.

8.4 Storage and handing instructions

Store below 30°C, Protected from light and moisture.

Keep the medicine out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Theon Pharmaceutical Ltd.

Village Saini Majra,

Tehsil Nalagarh, Distt. Solan (H.P.) - 174101

11. Details of permission or licence number with date

Mfg. Licence. No.: MNB/06/409 Issued on: 18.03.2024

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/GLUCRETA LM (5 mg+10 mg +500 mg) (5 mg+10 mg+1000 mg)/Mar-2024/01/PI