GLUCRETA SM

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

Abbreviated Prescribing information for **GLUCRETA SM**

(Dapagliflozin, Sitagliptin & Metformin Hydrochloride Extended Release Tablets) [Please refer the complete prescribing information for details].

PHARMACOLOGICAL PROPERTIES:

Mechanism of Action:

Sitagliptin: Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. *Dapagliflozin*: Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. *Metformin* may act via 3 mechanisms: 1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis. 2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization. 3) and delay of intestinal glucose absorption.

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

DOSAGE AND ADMINISTRATION: As directed by the Physician. Tablets should be taken orally.

CONTRAINDICATION: Diabetic pre-coma, Sever renal failure (GFR < 30 ml/min), Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock, Hepatic insufficiency, acute alcohol intoxication, alcoholism.

WARNINGS & PRECAUTIONS:

Sitagliptin: Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked. Bullous pemphigoid: There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, Sitagliptin should be discontinued.

Dapagliflozin: Dapagliflozin exposure is increased in patients with severe hepatic impairment. Use in patients at risk for volume depletion and/or hypotension Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations. In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately. Postmarketing 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. Elderly (≥ 65 years) Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. Urine laboratory assessments: Due to its mechanism of action, patients taking Dapagliflozin will test positive for glucose in their urine. *Metformin***:** Lactic acidosis: Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Renal function: Metformin is contraindicated in patients with GFR <30 ml / min and should be temporarily discontinued in presence of conditions that alter renal function. Cardiac function: Patients with heart failure are more at risk of hypoxia and renal insufficiency. Surgery: Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia

DRUG INTERACTIONS: It is especially important to mention to your doctor if you are taking: Medicines which increase urine production (diuretics), medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors such as ibuprofen and celecoxib). Certain medicines for the treatment of high Blood pressure (ACE inhibitors and angiotensin Il receptor antagonists). Beta-2 agonists such as salbutamol or Terbutaline (used to treat asthma). Corticosteroids (used to treat a variety of conditions such as severe inflammation Of the skin or in asthma). Medicines that may change the amount of Metformin in your blood especially if you Have reduced kidney function (such as verapamil, Rifampicin, cimetidine, dolutegravir, ranolazine, Trimethoprime, vandetanib, Isavuconazole, Crizotinib, olaparib). Other medicines used to treat diabetes. Metformin Film-coated Tablets with alcohol Avoid excessive alcohol intake while taking Metformin Film-coated Tablets since this may Increase the risk of lactic acidosis.

ADVERSE REACTIONS: *Sitagliptin***:** Common: low blood sugar, nausea, flatulence, vomiting. Uncommon: stomachache, diarrhoea, constipation, drowsiness. Rare: reduced number of platelet. *Dapagliflozin***:** Common: genital infection (thrush) of your penis or vagina (signs may include irritation, itching, unusual discharge or odour), back pain, passing more water (urine) than usual or needing to pass water more often, changes in the amount of cholesterol or fats in your blood (shown in tests), increases in the amount of red blood cells in your blood (shown in tests), decreases in creatinine renal clearance (shown in tests) in the beginning of treatment, dizziness, rash. Uncommon: loss of too much fluid from your body (dehydration, signs may include very dry or sticky mouth, passing little or no urine or fast heartbeat), thirst, constipation, awakening from sleep at night to pass urine, dry mouth, weight decreased, increases in creatinine (shown in laboratory blood tests) in the beginning of treatment, increases in urea (shown in laboratory blood tests)

*Metformin***:** Very common: Digestive problems such as feeling sick (nausea), being sick (vomiting), diarrhoea, bellyache (abdominal pain) and loss of appetite. Common: changes in taste. Very rare:

lactic acidosis. Abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes).

MARKETED BY:

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(Additional information is available on request)