Glysit® MET (Tablets)

30700
Ref. No: B2130700/23.12

Dapagliflozin Propanediol Monohydrate / SGLT2 inhibitors
Metformin HCL / Biguanides

GLYSIT® MET 5/500 TABLETS (FILM COATED)
GLYSIT® MET 5/1000 TABLETS (FILM COATED)

PRESENTATION:
Glysit® MET 5/500mg Film Coated Tablets: Orange, capsule shaped film coated tablet embossed 'COSMOS' on one side and plain on other side. Each film coated tablet contains: Dapagliflozin, Metformin and other excipients.
Glysit® MET 5/1000mg Film Coated Tablets: Orange, capsule shaped film coated tablet plain on one side with a breakline on other side. Each film coated tablet contains: Dapagliflozin, Metformin and other excipients.

CLINICAL PHARMACOLOGY:
Dapagliflozin
Dapagliflozin is another drug for type-2 diabetes mellitus. Its mechanism of action is to inhibit the glucose transporter (SGLT2) in the renal tubule, thus reducing resorption of glucose by this transporter, with the consequent reduced blood glucose.
Metformin HCL
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

PHARMACOKINETICS:
Dapagliflozin
Absorption
Dapagliflozin was rapidly and well absorbed after oral administration. Maximum Dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state Dapagliflozin Cmax and AUC values following once daily 10mg doses of Dapagliflozin were 158ng/mL and 628ng h/mL, respectively. The absolute oral bioavailability of Dapagliflozin following the administration of a 10mg dose is 78%. Administration with a high-fat meal decreased Dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Hence, Dapagliflozin can be administered with or without food.
Distribution
Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of Dapagliflozin was 118 litres.
Biotransformation
Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of Dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.
Elimination
The mean plasma terminal half-life (t½) for Dapagliflozin was 12.9 hours following a single oral dose of Dapagliflozin 10mg to healthy subjects. The mean total systemic clearance of Dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged Dapagliflozin. After administration of a 50mg [14C]-Dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

Metformin HCL
Absorption
After an oral dose of the prolonged release tablet, Metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours) .At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of Metformin prolonged release tablets is similar to that observed after administration of 1000mg of Metformin immediate release tablets b.i.d. Intrasubject variability of C_{max} and AUC of Metformin prolonged release is comparable to that observed with Metformin immediate release tablets. When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected). Mean Metformin absorption from the prolonged release formulation is almost not altered by meal composition. No accumulation is observed after repeated administration of up to 2000mg of Metformin as prolonged release tablets.
Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean VD ranged between 63-276L.
Metabolism
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination
Renal clearance of Metformin is > 400ml/min, indicating that Metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

USES:
Type 2 diabetes mellitus
It is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise. It is indicated to improve glycaemic control:
- in patients insufficiently controlled on their maximally tolerated dose of Metformin alone
- in combination with other medicinal products for the treatment of diabetes in patients insufficiently controlled with Metformin and these medicinal products
- in patients already being treated with the combination of Dapagliflozin and Metformin as separate tablets.

DOSAGE AND ADMINISTRATION:
One tablet twice every day OR as per physician's prescription. To be taken orally with or without food.

CONTRA-INDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.

Glysit® MET (Tablets)

ADVERSE EFFECTS/SPECIAL WARNINGS:
Dapagliflozin
Renal impairment
The glycaemic efficacy of Dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment
Hepatic impairment
There are limited clinical studies in patients with 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.
Diabetic ketoacidosis
Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of DKA.

Metformin HCL
Lactic acidosis:
Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to Metformin accumulation. Reported cases of lactic acidosis in patients on Metformin have occurred primarily in diabetic patients with significant renal failure.
Renal function:
As Metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels using the Cockcroft-Gault formula) should be determined before initiating treatment and regularly thereafter:
• At least annually in patients with normal renal function,
• at least two to four times a year in patients with creatinine clearance levels at the limit of normal and in elderly subjects.
Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an non-steroidal anti-inflammatory drug (NSAID).

OVERDOSAGE:
Dapagliflozin
Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500mg (50 times the maximum recommended human dose). These subjects are with no reports of dehydration, hypotension or electrolyte imbalance, and meaningful effect on QTc interval.
Metformin HCL
Hypoglycaemia has not been seen with Metformin Hydrochloride doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose of Metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and Metformin is hemodialysis.

INTERACTIONS:
Dapagliflozin
Diuretics
Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.
Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with Dapagliflozin in patients with type 2 diabetes mellitus. In patients with type 1 diabetes mellitus and a known risk of frequent or severe hypoglycaemia, it may be necessary to reduce the insulin dose at the time of initiating treatment with Dapagliflozin to decrease the risk of hypoglycaemia.

Metformin HCL
Concomitant use not recommended
Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.
Iodinated contrast agents
Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.
Combinations requiring precautions for use
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics.

PREGNANCY AND BREASTFEEDING:
Pregnancy: Due to limited data of use of Glysit® MET in pregnant women, the use of Glysit® MET is not recommended during pregnancy. When pregnancy is detected, treatment with Glysit® MET should be discontinued.
Breastfeeding: It is unknown whether Dapagliflozin and/or its metabolites are excreted in human milk and it is unknown whether Metformin is excreted in small amount in human breast milk. A risk to the new-borns/infants cannot be excluded therefore Glysit® MET should be discontinued during breastfeeding.

PHARMACEUTICAL PRECAUTIONS:
Store in a dry place below 30˚C. Protect from light. Keep all medicines out of the reach of children.
LEGAL CATEGORY:
Prescription Only Medicine (POM)

®Regd. TM

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