24300

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Glysit® Plus (Tablets)

Dapagliflozin propanediol monohydrate
Sodium-glucose co-transporter 2 (SGLT2) inhibitors and
Sitagliptin phosphate monohydrate
Dipeptidyl peptidase 4 (DPP-4) inhibitors

GLYSIT® PLUS 10/50MG TABLETS (FILM COATED)

GLYSIT® PLUS 10/100MG TABLETS (FILM COATED)

PRESENTATION:

Glysit® Plus 10/50mg Film Coated Tablets: Yellow, circular, biconvex film coated tablet embossed 'C' on one side and plain on the other side. Each film coated tablet contains: Dapagliflozin, Sitagliptin and other excipients.

Glysit® Plus 10/100mg Film coated Tablets: Yellow, round shaped film coated tablet plain on both sides. Each film coated tablet contains: Dapagliflozin, Sitagliptin 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.

Sitagliptin

Sitagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used in conjunction with diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus. The effect of this medication leads to glucose dependent increases in insulin and decreases in glucagon to improve control of blood sugar.

Pharmacokinetics:

Dapagliflozin

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum Dapagliflozin plasma concentrations (Cmax) 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 158 ng/mL and 628 ng 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 Cmax by up to 50% and prolonged Tmax 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 metabolised, 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 (t1/2) 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.

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, Sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose. The absolute bioavailability of Sitagliptin is approximately 87%. Since co-administration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics, Januvia may be administered with or without food. Plasma AUC of Sitagliptin increased in a dose-proportional manner.

Distribution

The mean volume of distribution at steady state following a single 100mg intravenous dose of Sitagliptin to healthy subjects is approximately 198 litres. The fraction of Sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of Sitagliptin is excreted unchanged in the urine.

Following a Sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of Sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of Sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of Sitagliptin was CYP3A4, with contribution from CYP2C8.

Elimination

Following administration of an oral Sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing.

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

Type 1 diabetes mellitus: It is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI $\geq$ 27 kg/m2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

DOSAGE AND ADMINISTRATION:

Glysit® Plus (Tablets)

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

CONTRA-INDICATIONS AND WARNINGS:
Hypersensitivity to the active substance or to any of the excipients.
Adverse effects:
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.
Sitagliptin
Acute pancreatitis: Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis. persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of Sitagliptin but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported.
Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products: Hypoglycaemia has been observed when Sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered.
Renal impairment: Sitagliptin is renally excreted. To achieve plasma concentrations of Sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR $<$ 45 mL/min. 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 reports of bullous pemphigoid in patients taking DPP-4 inhibitors including Sitagliptin. If bullous pemphigoid is suspected, Glysit® Plus should be discontinued.
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.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of Dapagliflozin by haemodialysis has not been studied.
Sitagliptin
There is no experience with doses above 800 mg in clinical studies.
Sitagliptin is modestly dialysable. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialysable by peritoneal dialysis. 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 (including obtaining an electrocardiogram), and institute supportive therapy if required.
In clinical studies, approximately 13.5 % of the dose was removed over a 3-4 hour haemodialysis session.
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. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.
Sitagliptin
Effects of Sitagliptin on other medicinal products
Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25mg digoxin concomitantly with 100mg of Sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11% and the plasma Cmax on average by 18%. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when Sitagliptin and digoxin are administered concomitantly.
Pregnancy and Breast-Feeding:
Pregnancy: There are no data from the use of Dapagliflozin in pregnant women. When pregnancy is detected, treatment with Dapagliflozin should be discontinued.
Breast-feeding: It is unknown whether Dapagliflozin and/or its metabolites are excreted in human milk. A risk to the new-borns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

PHARMACEUTICAL PRECAUTIONS: Store in a dry place below 30ºC. Protect from light. Keep all medicines out of the reach of children.

LEGAL CATEGORY: Prescription Only Medicine (POM)

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COSMOS

Cosmos Limited,
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