1.6.3 Patient information leaflet (PIL)

DYGLI-M® TABLETS

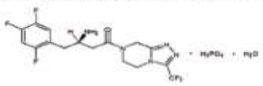
Sitagliptin and metformin hydrochloride tablets 50/500 & 50/1000 mg)

COMPOSITION: Each film coated tablet contains: Sitagliptin Phosphate (as Monohydrate) USP equivalent to Sitagliptin 50 mg, Metformin Hydrochloride BP 500 mg

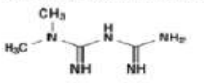
Each film coated tablet contains: Sitagliptin Phosphate (as Monohydrate) USP equivalent to Sitagliptin 50 mg, Metformin Hydrochloride BP 1000 mg

DESCRIPTION: DYGLI – M Tablets contain two oral anti hyperglycemic drugs (Sitagliptin and Metformin hydrochloride) used in the management of type 2 diabetes

Sitagliptin: Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin is present in tablets in the form of Sitagliptin phosphate monohydrate. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate with an empirical formula of $C_{16}H_{15}F_6N_5O_4P \cdot H_2O$ and a molecular weight of 523.32. The structural formula is:



Metformin hydrochloride: Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



MECHANISM OF ACTION: DYGLI – M combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class

Sitagliptin: Sitagliptin is a DPP- 4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by Sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. 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 by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses

Metformin Hydrochloride: Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic Group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs

ATC CodeA10BD07

DYGLI – M Co-administration: In a two-day study in healthy subjects, Sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of Sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes. In studies with healthy subjects, Sitagliptin did not lower blood glucose or cause hypoglycemia

PHARMACOKINETICS: The results of a bioequivalence study in healthy subjects demonstrated that the DYGLI – M combination tablets are bioequivalent to co-administration of corresponding doses of Sitagliptin and Metformin hydrochloride as individual tablets

ABSORPTION:

Sitagliptin: The absolute bioavailability of Sitagliptin is approximately 87%. Co-administration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics of Sitagliptin

Metformin hydrochloride: The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax)

DISTRIBUTION:

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

Metformin hydrochloride: The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time

METABOLISM:

Sitagliptin: Approximately 79% of Sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Following 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

Metformin hydrochloride: Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion

EXCRETION:

Sitagliptin: Following administration of an oral [14C] Sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal t1/2 following a 100-mg oral dose of Sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min

Metformin hydrochloride: Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution

INDICATIONS:

DYGLI – M is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both Sitagliptin and metformin is appropriate also is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea

DYGLI – M is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma ($PPAR_\gamma$) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a $PPAR_\gamma$ agonist

DYGLI – M is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control

DOSAGE:

Recommended Dosing: The dosage of DYGLI – M should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg Sitagliptin and 2000 mg metformin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider. DYGLI – M should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. The starting dose of DYGLI – M should be based on the patient's current regimen. DYGLI – M should be given twice daily with meals. The recommended starting dose in patients not currently treated with metformin is 50 mg Sitagliptin/500 mg metformin hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin. The starting dose in patients already treated with metformin should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. Patients treated with an insulin secretagogue or insulin Co-administration of DYGLI – M with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia. No studies have been performed specifically examining the safety and efficacy of DYGLI – M in patients previously treated with other oral antihyperglycemic agents and switched to DYGLI – M. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur

CONTRAINDICATION:

DYGLI – M is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients used in the formulations;
- diabetic ketoacidosis, diabetic pre-coma;
- moderate and severe renal impairment (creatinine clearance < 60 mL/min);
- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, - intravascular administration of iodinated contrast agent
- acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock;
- hepatic impairment;
- acute alcohol intoxication, alcoholism;
- breast-feeding

DYGLI – M should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function

DYGLI – M should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings

DYGLI – M has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis

PRECAUTIONS AND WARNINGS:

Cases of inflammation of the pancreas (pancreatitis) have been reported. Pancreatitis, gallstones, alcoholism or very high triglycerides can increase of getting pancreatitis or getting it again. Type -1 diabetics. Experience some of the following symptoms: feeling cold or uncomfortable, severe nausea or vomiting, abdominal pain, unexplained weight loss, muscular cramps, or rapid breathing. Metformin hydrochloride can cause a rare but serious side effect called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Allergic reaction to DYGLI – M. Sulphonyl ureas or insulin, diabetes medicines, together with tablet as may experience low blood sugar levels (hypoglycaemia). Need to stop taking Sitagliptin and Metformin tablets for a couple of days before and after the operation under general, spinal or epidural anaesthetic

Children and adolescents: Children and adolescents below 18 years should not use this medicine. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age

Use in Pregnancy: Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women with DYGLI – M or its individual components; therefore, the safety of Sitagliptin and Metformin Hydrochloride in pregnant women is not known. Sitagliptin and Metformin should be used during pregnancy only if clearly needed

Lactation: Sitagliptin and metformin Hydrochloride are secreted in the milk of lactating rats. It is not known whether Sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Sitagliptin and Metformin Hydrochloride is administered to a nursing woman

Effects on ability to drive and use machines: Sitagliptin and Metformin Hydrochloride has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolences have been reported with Sitagliptin

DRUG INTERACTIONS:

The following medicines are particularly important:

- Medicines (taken by mouth, inhalation, or injection) used to treat diseases that involve inflammation, like asthma and arthritis (corticosteroids)
- Specific medicines for the treatment of high blood pressure (ACE inhibitors)
- Medicines which increase urine production (diuretics)
- Specific medicines for the treatment of bronchial asthma (beta-sympathomimetics)
- Iodinated contrast agents or alcohol- containing medicines
- Certain medicines used to treat stomach problems such as cimetidine
- Digoxin (to treat irregular heart beat)

ADVERSE EFFECTS: Like all medicines, this medicine can cause side effects, although not everybody gets them. Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Sitagliptin and Metformin Hydrochloride tablets. Pancreatitis can be a serious, potentially life-threatening medical condition. Stop taking the medicine when experience severe and persistent stomach pain, with or without vomiting. Very rarely (may affect up to 1 in 10,000 people) patients have experienced a serious condition called lactic acidosis. This is more common in people whose kidneys are not working properly. Stop taking medicine when the following symptoms occur:

- Feeling sick (nausea) or being sick (vomiting), stomachache (Abdominal pain), muscular cramps, unexplained weight loss, rapid breathing, and feeling cold or uncomfortable. Serious allergic reaction including rash, hives and swelling of the face, lips, tongue and throat that may cause difficulty in breathing or swallowing, stop taking this medicine. Some patients taking metformin have experienced the following side effects after starting Sitagliptin, common (may affect up to 1 in 10 people), low blood sugar, nausea, flatulence, vomiting. Uncommon (may affect up to 1 in 100 people), stomachache, diarrhoea, constipation, drowsiness. Some patients have experienced diarrhoea, nausea, flatulence, constipation, stomachache or vomiting when starting the combination of Sitagliptin and metformin Hydrochloride together

OVERDOSAGE AND TREATMENT: In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with Sitagliptin with doses of up to 400 mg per day for periods of up to 28 days. 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 as indicated by the patient's clinical status. Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis. Overdose of Metformin Hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with Metformin Hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of Metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom Metformin over dosage is suspected

STORAGE: Store in the original package below 30°C. Keep out of reach of children

PRESENTATIONS: PVC Aluminium Blister Pack of 3 x 10 Tablets

Shelf life: 2 Years

DATE OF PUBLICATION OR REVIEW: July 1st,2019

PRISMA
A RAY OF HOPE

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BPT 486 LF

Length (210mm) x Height (297mm)