QOSMET

COMPOSITION:

Each tablet of QOSMET 500/50mg contains:
Metformin……500 mg
Sitagliptin……..50 mg
Each tablet of QOSMET 1gm/50mg contains:
Metformin……..……..1gm
Sitagliptin……..50mg

DESCRIPTION:

Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin is present in QOSMET 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]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine phosphate (1:1) monohydrate with an empirical formula of C16H15F6N5O.H3PO4.H2O and a molecular weight of 523.32. 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 C4H11N.HCl 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:

INDICATIONS:

QOSMET 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.

MECHANISM OF ACTION:

Combination products containing metformin and Sitagliptin are used to improve hypoglycemic effects.
Metformin: Metformin decreases hepatic gluconeogenesis, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization; insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease. Metformin improve glucose utilization in skeletal muscle and adipose tissue by increasing cell membrane glucose transport. This effect is may be due to improved binding of insulin to insulin receptors since metformin is not effective in diabetics without some residual functioning pancreatic islet cells. Metformin causes 10-20% decrease in fatty-acid oxidation and a slight increase in glucose oxidation. Unlike phenformin, metformin does not inhibit the mitochondrial oxidation of lactate unless its plasma concentrations become excessive (i.e., in patients with renal failure) and/or hypoxia is present. Clinically, metformin lowers fasting and postprandial hyperglycemia. The decrease in fasting plasma glucose is approximately 25-30%. Unlike oral sulfonylureas, it rarely causes hypoglycemia. Thus metformin demonstrate more of an anti-hypertensive action than a hypoglycemia action. Metformin dose not cause weight gain, in fact, may cause a modest weight loss due to drug-induced anorexia. Metformin also decreases plasma VLDL triglycerides resulting in modest decreases in plasma triglycerides and total cholesterol.

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Patients receiving metformin show a significant improvement in hemoglobin A1c, and a tendency toward improvement in the lipid profile, especially when baseline values are abnormally elevated.
Sitagliptin: Sitagliptin is a dipeptidyl peptidase-IV (DPP-IV) inhibitor, which exerts 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-IV. Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.
GLP-1 does not increase insulin secretion when the glucose concentration is < 90 mg/dl. The contributions of GIP, which increases insulin secretion and regulates fat metabolism, to the overall effects of Sitagliptin are unclear at this time. Sitagliptin is of benefit in patients with type 2 diabetes mellitus as their GLP-1 concentrations are decreased in response to a meal. The long term safety of DPP-IV inhibitors are currently under investigation as DPP-IV is not an enzyme specific for the breakdown of incretin hormones.

PHARMACOKINETICS:

Metformin: Sitagliptin is administered orally as an immediate-release tablet. Bioequivalence studies indicate that metformin- Sitagliptin is bioequivalent to coadministration of Sitagliptin and metformin as single agents.
Metformin: Metformin is distributed rapidly into peripheral body tissues and fluids and appears to distribute slowly into erythrocytes and to a deep tissue compartment (most likely GI tissues). The highest concentrations of metformin are found in the GI tract (10 times the concentrations in the plasma) and lower concentrations in the kidney, liver, and salivary gland tissue. Metformin does not bind to hepatic or plasma proteins. It is not metabolized by the liver, which may explain why the risk of lactic acidosis is much less for metformin than for phenformin. About 90% of a dose is excreted by the kidneys, largely unchanged, through an active tubular process.
Tubular secretion may be altered by many cationic drugs. Approximately 10% of an oral dose is excreted in the feces, presumably as unabsorbed metformin. Although the average elimination half-life in the plasma is 6.2 hours in patients with normal renal function, metformin is distributed to and accumulates in red blood cells, which leads to a much longer elimination half-life in the blood (17.6 hours).
Sitagliptin: Sitagliptin is not highly bound to plasma proteins (38%). Metabolism is a minor pathway of elimination with approximately 16% of a dose excreted as metabolites. Six metabolites have been detected at trace concentrations and are not expected to contribute significantly to Sitagliptin activity. The primary enzymes responsible for metabolism are CYP3A4 and CYP2C8. Elimination occurs primarily via renal excretion and involves active tubular secretion; approximately 79% of a dose is excreted unchanged in the urine. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating renal elimination. The apparent terminal half-life of Sitagliptin 100 mg is 12.4 hours. One-hundred percent of an administered dose is excreted in the urine (87%) or feces (13%) within 1 week of dosing.

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DOSAGE AND ADMINISTRATION:

The dosage of QOSMET 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.
QOSMET 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 QOSMET should be based on the patient's current regimen. QOSMET 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 dose as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose of QOSMET is 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.
Patients treated with an insulin secretagogue or insulin
Co-administration of QOSMET 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 QOSMET in patients previously treated with other oral antihyperglycemic agents and switched to QOSMET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

WARNINGS & PRECAUTIONS:

Hepatic Impairment:
Specific pharmacokinetic studies have not been performed in patients with hepatic dysfunction receiving metformin: Sitagliptin, but hepatic impairment may increase the risk of lactic acidosis.
Renal Impairment:
Avoid use in those with renal disease. Metformin will accumulate in patients with CrCl < 60 ml/min; this may increase the risk of lactic acidosis. In patients with moderate (CrCl 30-50 ml/min) or severe (< 30 ml/min or on dialysis) renal impairment, the plasma AUC of Sitagliptin increases 2-fold and 4-fold, respectively. Metformin is removed by hemodialysis.
Geriatric:
The pharmacokinetics of Sitagliptin in elderly patients is not significantly different when compared to younger patients; however, age-related decreases in renal function may result in metformin accumulation.

CONTRAINDICATIONS:

QOSMET 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.
QOSMET 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 while using QOSMET.

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ADVERSE REACTIONS:

- The most common adverse reactions reported in >5% of patients simultaneously started on Sitagliptin and metformin and more commonly than in patients treated with placebo were diarrhea, upper respiratory tract infection, and headache.
- Adverse reactions reported in >5% of patients treated with Sitagliptin in combination with sulfonylurea and metformin and more commonly than in patients treated with placebo in combination with sulfonylurea and metformin were hypoglycemia and headache.
- Nasopharyngitis was the only adverse reaction reported in >5% of patients treated with Sitagliptin monotherapy and more commonly than in patients given placebo.
- The most common (>5%) adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

STORAGE:

Do not Store above 30°C.
Keep in a dry place.

PRESENTATION:

QOSMET tablet 500/50mg is presented in a blister pack of 10 tablets
QOSMET tablet 1gm/50mg is presented in a blister pack of 10 tablets