Siglimet™

Sitagliptin & Metformin Hydrochloride

COMPOSITION

Siglimet™ 50/500 Tablet: Each film coated tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate Monohydrate USP and Metformin Hydrochloride Ph. Eur. 500 mg. **Siglimet**™ 50/1000 Tablet: Each film coated tablet contains Sitagliptin 50 mg as Sitagliptin Phosphate Monohydrate USP and Metformin Hydrochloride Ph. Eur. 1000 mg.

PHARMACOLOGY

Siglimet™ combines 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 is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin 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. The pharmacologic mechanism of action of Metformin is different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose,and increases peripheral glucose uptake and utilization.

INDICATION AND USAGE

Siglimet™ 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.

DOSAGE AND ADMINISTRATION

Dose of this combination 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. Sitagliptin/Metformin combination should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to Metformin. 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. For patients taking Metformin 850 mg twice daily, the recommended starting dose of this combination is 50 mg Sitagliptin/1000 mg Metformin hydrochloride twice daily.
Patients treated with an insulin secretagogue or insulin: Co-administration of the combination 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.

PRECAUTIONS

Do not use the combination of Sitagliptin & Metformin in patients with hepatic disease.
* Before initiating the combination and at least annually thereafter, assess renal function and verify as normal.
* May need to discontinue the combination and temporarily use insulin during periods of stress and decreased intake of fluids and food as may occur with fever, trauma, infection or surgery.

CONTRAINDICATIONS

Combination (Sitagliptin/Metformin HCl) is contraindicated in patients with:
* Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels 1.5 mg/dL [males], 1.4 mg/dL [females].
* Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.
* History of a serious hypersensitivity reaction to the combination or sitagliptin, such as anaphylaxis or angioedema.

ADVERSE EFFECTS

The most common (>5%) adverse reactions due to initiation of Metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

DRUG INTERACTION

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine,triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renaltubular transport systems. Co-administration of Digoxin and Sitagliptin may slightly increase the mean peak drug concentration of Digoxin. But no dosage adjustment of digoxin or Sitagliptin is recommended.

USE IN PREGNANCY & LACTATION: PREGNANCY

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

NURSING MOTHERS

It is not known whether Sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when this combination is administered to a nursing woman.

GERIATRIC USE

Because Sitagliptin and Metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, combination of Sitagliptin and Metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

PEDIATRIC USE

Safety and effectiveness of Sitagliptin/Metformin in pediatric patients under 18 years of age have not been established

STORAGE

Store below 30^{O} C, in a dry place. Keep all medicines out of reach of children.

HOW SUPPLIED

Siglimet™ 50/500 Tablet: Each box contains 30 tablets in blister pack.
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Manufactured by

SQUARE
PHARMACEUTICALS PLC.
BANGLADESH