

Glyros

Glimepiride and Rosiglitazone

Composition

Glyros® 1: Each film coated tablet contains Glimepiride INN 1 mg and Rosiglitazone 4 mg as Rosiglitazone maleate INN.

Glyros® 2: Each film coated tablet contains Glimepiride INN 2 mg and Rosiglitazone 4 mg as Rosiglitazone maleate INN.

Pharmacology

Glyros® combines 2 antidiabetic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes:

Glimepiride, a member of the sulfonylurea class, and Rosiglitazone maleate, a member of the thiazolidinedione class. The primary mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta-cells. In addition, extrapancreatic effects may also play a role in the activity of sulfonylureas such as Glimepiride. This is supported by both preclinical and clinical studies demonstrating that Glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin.

Thiazolidinediones are insulin-sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas sulfonylureas act primarily by stimulating release of insulin from functioning pancreatic beta-cells. Rosiglitazone improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR γ). Activation of PPAR γ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPAR γ -responsive genes also participate in the regulation of fatty acid metabolism.

Indication and usage

Glyros® (Combination of Glimepiride and Rosiglitazone) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of Rosiglitazone and sulfonylurea as separate tablet or who are not adequately controlled on a sulfonylurea alone or for those patients who have initially responded to Rosiglitazone alone and require additional glycemic control.

Dosage and administration

Glyros® should be given once daily with the first meal of the day. The dosage of antidiabetic therapy with Glyros® should be individualized on the basis of effectiveness and tolerability. No exact dosage relationship exists between Glyros® and other antidiabetic agents.

For patients inadequately controlled on sulfonylurea monotherapy or who have initially responded to Rosiglitazone alone and require additional glycemic control, the usual starting dose of Glyros® is 1 mg/4 mg or 2 mg/4 mg once daily.

When switching from combination therapy of Glimepiride plus Rosiglitazone as separate tablets, the usual starting dose of Glyros® is the dose of Glimepiride and Rosiglitazone already being taken. The maximum recommended daily dose of Glyros® is 4 mg of Glimepiride and 8 mg of Rosiglitazone.

Sufficient time should be given to assess adequacy of therapeutic response. Fasting glucose should be used to determine the therapeutic response to Glyros®.

For patients previously treated with sulfonylurea monotherapy switched to Glyros®, it may take 2 weeks to see a reduction in blood glucose and 2 to 3 months to see the full effect of the Rosiglitazone component. If additional glycemic control is needed, the dose of the

Glimepiride component may be increased. The dose of the Rosiglitazone component should not exceed 8 mg. As with other sulfonylurea-containing antidiabetic agents, no transition period is necessary when transferring patients to Glyros®. Patients should be observed carefully (1 to 2 weeks) for hypoglycemia when being transferred from longer half life sulfonylureas (e.g., chlorpropamide) to Glyros® due to potential overlapping of drug effect. For patients previously treated with thiazolidinedione monotherapy switched to Glyros® dose titration is recommended if patients are not adequately controlled after 1 to 2 weeks. If additional glycemic control is needed, the daily dose of Glyros® may be increased by increasing the Glimepiride component in no more than 2 mg increments at 1- to 2-week intervals up to the maximum recommended total daily dose of 4 mg Glimepiride/8 mg Rosiglitazone.

If hypoglycemia occurs during up-titration of the dose or while maintained on therapy, a dosage reduction of the sulfonylurea component of Glyros® may be considered.

Precautions

General: Due to the mechanisms of action, Rosiglitazone is active only in the presence of endogenous insulin. Therefore, combination of Glimepiride and Rosiglitazone should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. **Hypoglycemia:** Glyros® is a combination tablet containing Glimepiride and Rosiglitazone. All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly patients are particularly susceptible to hypoglycemic action of glucose lowering drugs. Debilitated or malnourished patients and those with adrenal, pituitary, renal, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose lowering drugs. **Loss of Control of Blood Glucose:** When a patient stabilized on any antidiabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold combination of Glimepiride and Rosiglitazone and temporarily administer insulin. Combination of Glimepiride and Rosiglitazone may be reinstated after the acute episode is resolved. **Edema:** Combination of Glimepiride and Rosiglitazone should be used with caution in patients with edema. Since thiazolidinediones, including Rosiglitazone can cause fluid retention, which can exacerbate or lead to congestive heart failure, combination of Glimepiride and Rosiglitazone should be used with caution in patients at risk for heart failure. **Weight Gain:** Dose-related weight gain was seen with Rosiglitazone alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation. **Hepatic Effects:** Liver enzymes should be checked prior to the initiation of therapy with combination of Glimepiride and Rosiglitazone in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with combination of Glimepiride and Rosiglitazone should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with combination of Glimepiride and Rosiglitazone, liver enzyme levels should be rechecked as soon as possible.

If ALT levels remain >3X the upper limit of normal, therapy with combination of Glimepiride and Rosiglitazone should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, and anorexia, and/or dark urine, liver enzymes should be checked.

Contraindications

Combination of Glimepiride and Rosiglitazone is contraindicated in patients with known hypersensitivity to Glimepiride or Rosiglitazone or any of the components of combination of Glimepiride or Rosiglitazone. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

Use in Pregnancy

Pregnancy Category C. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible. Combination of Glimepiride or Rosiglitazone should not be used during pregnancy. Nursing mothers: No studies have been conducted with combination of Glimepiride or Rosiglitazone. It is not known whether Glimepiride and/or Rosiglitazone is excreted in human milk. Because many drugs are excreted in human milk, combination of Glimepiride or Rosiglitazone should not be administered to a nursing woman.

Use in Pediatric patients

Safety and effectiveness of combination of Glimepiride or Rosiglitazone in pediatric patients have not been established.

Use in Geriatric patients

Glimepiride: The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Rosiglitazone: Results of the population pharmacokinetic analysis showed that age does not significantly affect the pharmacokinetics of Rosiglitazone. Therefore, no dosage adjustments are required for the elderly.

Adverse effects

Glimepiride: Hypoglycemia: The incidence of hypoglycemia with Glimepiride is documented. In patients treated with Glimepiride, adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in more than 1% of patients included dizziness, asthenia, headache, and nausea. Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of Glimepiride. Rosiglitazone: The most common adverse experiences with Rosiglitazone monotherapy were upper respiratory tract infection, injury, and headache. Overall, the types of adverse experiences reported when Rosiglitazone was used in combination with a sulfonylurea were similar to those during monotherapy with Rosiglitazone. Events of anemia and edema tended to be reported more frequently at higher doses, and were generally mild to moderate in severity and usually did not require discontinuation of treatment with Rosiglitazone. Angioedema and urticaria have been reported rarely with Rosiglitazone treatment.

Drug interactions

Glimepiride: Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid. When these drugs are administered to a patient receiving Glimepiride, the patient should be closely observed for loss of control. When these drugs are withdrawn from a patient receiving Glimepiride, the patient should be observed closely for hypoglycemia. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of miconazole is not known. Potential interactions of Glimepiride with other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid. Rosiglitazone: Drugs Metabolized by Cytochrome P450: An inhibitor of CYP2C8 (such as gemfibrozil) may increase the AUC of

Rosiglitazone and an inducer of CYP2C8 (such as rifampin) may decrease the AUC of Rosiglitazone. Therefore, if an inhibitor or an inducer of CYP2C8 is started or stopped during treatment with Rosiglitazone, changes in diabetes treatment may be needed based upon clinical response.

Storage

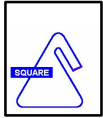
Store in a cool and dry place. Protect from light and moisture. Keep out the reach of the children.

How supplied

Glyros® 1: Each box contains 3 x 10's tablet in blister pack.

Glyros® 2: Each box contains 3 x 10's tablet in blister pack.

Manufactured by:



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PHARMACEUTICALS LTD.
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