SAROZAR

Saroglitazar INN

COMPOSITION

Sarozar 2 Tablet: Each film coated tablet contains Saroglitazar Magnesium INN equivalent to Saroglitazar 2 mg.

THERAPEUTIC CLASS

Glitazars (PPAR-α and -γ dual agonist)

CLINICAL PHARMACOLOGY

Mechanism of Action: Saroglitazar is a potent and predominantly Peroxisome Proliferator-Activated Receptor (PPAR)-alpha agonist with moderate PPAR-gamma agonistic activity. PPARs are nuclear lipid-activated transcription factors that regulate the expression of various genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes.

PPARα activation by Saroglitazar increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of TG. This in turn increases diversion of FA from peripheral tissues (e.g. skeletal muscle and fat tissue) to the liver, and thereby decreasing both FA synthesis and delivery of TG to peripheral tissues. Saroglitazar also causes increased lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase (LPL) and reducing production of apolipoprotein C-III (an inhibitor of LPL activity). Consistent with the above mechanism, Saroglitazar was also found to reduce plasma LDL cholesterol. PPARα activation by Saroglitazar also induces an increase in the synthesis of apolipoproteins A-I, A-II and HDL-cholesterol. Although Saroglitazar is predominantly a PPARα agonist, it also causes activation of PPARγ and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Saroglitazar increases the expression of numerous PPARγ-responsive genes involved in carbohydrate and lipid metabolism, including adiponectin, adipocyte fatty-acid-binding protein (aP2), LPL, fatty acid transport protein (FATP) and fatty acid translocase (CD36). By increasing the expression of these genes, Saroglitazar decreases the post prandial rise of plasma free fatty acids, improves post-absorptive insulin-mediated suppression of hepatic glucose output, reduces the metabolic burden on liver & muscle and promotes glucoseutilization. Robust anti-diabetic and insulin sensitizing effects of Saroglitazar were observed in preclinical models, in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues.

Pharmacodynamics: The effects of Saroglitazar at a dose of 4 mg per day were assessed in two Phase-III randomized, double-blind, parallel-group studies including diabetic patients with Triglycerides >200 mg/dL. In one study, the patients were treated with Saroglitazar 4 mg or Pioglitazone (45 mg) for 24 weeks. When compared to Pioglitazone, Saroglitazar 4 mg achieved the ATP III goal in more subjects.

In another study, the effect of Saroglitazar at 4 mg per day was assessed in diabetic patients with hypertriglyceridemia not controlled with Atorvastatin 10 mg therapy. The patients were treated with Saroglitazar 4 mg or placebo for 12 weeks along with Atorvastatin 10 mg. In combination with Atorvastatin, Saroglitazar achieved the ATP-III goal in more subjects than Atorvastatin alone; hence demonstrating better cardiovascular risk reduction.

Saroglitazar has also shown a decrease in TG, LDL, VLDL, non-HDL cholesterol and TC with an increase in HDL in non-diabetic patients. No hypoglycemia incidence was reported during Phase I-III trials in both diabetic and non-diabetic subjects.

Pharmacokinetics: The single-dose pharmacokinetics of Saroglitazar was assessed across the dose range of 0.125 to 128 mg.

Absorption: Following oral administration in healthy volunteers, peak plasma levels of Saroglitazar occurred at approximately 1-hour post-dosing in both genders. The maximum plasma concentration (Cmax) and area under the curve (AUC0-) of Saroglitazar increased proportionally with the administered single doses of 0.125 mg - 128 mg daily. After single oral dose of Saroglitazar 4 mg in healthy volunteers, Cmax of 337.1 ± 91.0 ng/ml (Mean ± SD, n=6) was observed. Pooled analysis of male and female healthy volunteers showed no gender effect or food effect on the pharmacokinetics of Saroglitazar.

Distribution: The mean apparent oral volume of distribution (Vd/F) of Saroglitazar following single-dose administration of Saroglitazar 4 mg was 20.14 ± 6.92 L. In vitro Saroglitazar is extensively protein bound (~ 96%) in human plasma. The mean plasma half-life of Saroglitazar following single-dose administration of Saroglitazar 4 mg is 2.9 ± 0.9 hours. Multiple-dose studies in humans have shown that Saroglitazar does not undergo accumulation on repeat dosing once daily for 10 days.

Metabolism: In healthy volunteers, Saroglitazar 4 mg has an apparent oral clearance, CL/F, calculated to be 4.8 ± 0.93 L/hr. In vitro studies using pooled human liver microsomes showed that Saroglitazar is metabolically stable. Following Saroglitazar 4 mg administration, Saroglitazar was found to be metabolized into three minor oxidative metabolites. The exposure of the most abundant oxidative metabolite was found to be less than 10% of the exposure of Saroglitazar.

Excretion: In healthy volunteers, Saroglitazar was not excreted in the urine indicating that it has non-renal route of elimination. Preclinical studies have shown that Saroglitazar is predominantly eliminated unchanged by the hepatobiliary route.

INDICATIONS AND USAGE

Saroglitazar is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy. In clinical studies, Saroglitazar has demonstrated reduction of triglycerides (TG), Low Density Lipoprotein (LDL) cholesterol, Very Low Density Lipoprotein (VLDL) cholesterol, non - High Density Lipoprotein (non- HDL) cholesterol and an increase in HDL cholesterol. It has also shown favorable glycemic indices by reducing the fasting plasma glucose and glycosylated hemoglobin in diabetic patients.

DOSAGE AND ADMINISTRATION

The recommended dose of Saroglitazar is two tablets of 2 mg once a day.

ADVERSE EVENTS

In two controlled phase III clinical studies of 12 to 24 weeks treatment duration with Saroglitazar, the most common adverse events (AEs ≥ 2%) reported were gastritis, asthenia and pyrexia. Most of the AEs were mild to moderate in nature and did not result in discontinuation of the study.

Because clinical studies are conducted under widely varying conditions, AE rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

CONTRAINDICATIONS

Hypersensitivity to Saroglitazar or any of the excipients used in the formulation.

DRUG INTERACTIONS

In vitro studies using recombinant human cytochrome P-450 (CYP) isozymes indicate that Saroglitazar does not significantly inhibit CYP1A2, 2C9, 2C19, 2D6 and 3A4 at concentrations of 10μM. Similarly, Saroglitazar did not show any potential for CYP3A4 enzyme induction when tested up to 100 μM concentration in a luciferase-based reporter assay in transiently transfected HepG2 cells. Although no clinical drug-drug interaction studies have been conducted with Saroglitazar so far, because the tested concentrations (10 μM and 100 μM) are several times higher than the mean C max of Saroglitazar, it can be inferred that Saroglitazar would not cause clinically significant drug-drug interactions related to the above-evaluated CYPs.

PRECAUTIONS

Although clinical studies with Saroglitazar have not demonstrated any potential for myopathies or derangement of liver and/or renal function, Saroglitazar treatment should be initiated with caution in patients with abnormal liver or renal function, or history of myopathies.

Saroglitazar has not been studied in patients with established New York Heart Association (NYHA) Class III or IV heart failure. Saroglitazar should be initiated with caution in patients with type 2 diabetes having cardiac disease with episodic congestive heart failure and such patients should be monitored for signs and symptoms of congestive heart failure.

Although no significant weight gain and edema were reported with Saroglitazar during the clinical studies, patients who experience rapid increases in weight should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category C

The safety of Saroglitazar in pregnant women has not been established as there is no adequate and well-controlled study carried out in pregnant women. Women who become pregnant during Saroglitazar treatment should contact their physicians. Saroglitazar should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Nursing mothers should not use Saroglitazar because it is not known whether Saroglitazar is excreted into breast milk.

Pediatric Use

The safety and effectiveness of Saroglitazar in children less than 18 years of age have not been established.

Geriatric Use

Considering the comorbidity and concomitant medications in elderly patients, Saroglitazar should be used with caution in geriatric patients.

OVERDOSE

During clinical studies, no incidence of overdose with Saroglitazar has been reported. In case of overdose with Saroglitazar, general supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status.

PHARMACEUTICAL INFORMATION

Storage condition

Store below 25^0 C and dry place, away from light and moisture. Keep out of the reach of children.

Packaging

Sarozar 2 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister.

Manufactured By

Beacon Pharmaceuticals PLC

Bhaluka, Mymensingh, Bangladesh

LF47201