## Drug Update

# Saroglitazar (Lipaglyn)

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**ABSTRACT**

Atherogenic diabetic dyslipidemia (ADD) is an important CVD risk factor. Indians are at higher risk of ADD due to genetic, dietary and lifestyle factors. Though statins reduce CV complications in diabetic patients by 20-30%, a significant residual CV risk remains a concern. Hypertryglyceridemia is one of the important cause for this residual risk. PPAR-γ agonists are effective insulin sensitizers and they when administered with metformin, helps to achieve glycemic control. Both PPAR-α and PPAR-γ agonists have shown benefits individually in diabetic patients. So, there is a possibility that dual PPAR-α/γ agonists can improve CV outcomes with lesser side effects in diabetic patients. Lipaglyn is a novel dual PPAR-α/γ agonist with 1000 times more selectivity for PPAR-α over PPAR-γ. Lipaglyn is the first PPAR dual agonist to be approved in the world.

**Introduction -**

Every fourth diabetic in the world is an Indian. As per an ICMR study in 2011, the prevalence of diabetes has increased to 12-18% in urban India, 3-65 in rural India and another 14% having pre-diabetes.

Diabetics have an increased cardiovascular risk. This risk gets exaggerated by lipid abnormalities additionally. Diabetics have an increased propensity to develop dyslipidemia (also known as 'Atherogenic Diabetic Dyslipidemia' - ADD) characterized by high TG and / or low HDL-C and or small dense LDL-C. Indian type 2 diabetics are highly prone to be dyslipidemic as a study found that 85.5% male, and as high as 97.2% female Indian diabetics have dyslipidemia.

Diabetes and its accompanying dyslipidemia is traditionally managed by using combinations of various anti-diabetic and lipid lowering drugs. Anti-diabetic drugs have various adverse effects ranging from hypoglycemia, exhaustion of the pancreatic beta cells, fluid retention to congestive cardiac failure. Lipid lowering agents like statins and fibrates can pose hazard of muscle toxicity.

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PPAR-α agonist (fenofibrate) and PPAR-γ agonist (pioglitazone) are approved respectively for lipid control and glycemic control in type 2 diabetes. However increasing concerns with thiazolinediones with regard to fluid retention, weight gain and congestive cardiac failure have resulted in new label warning for these agents. Hence, there was a strong need for a dual PPAR-α/γ agonist with beneficial effects in controlling both lipids and glycemic levels with all necessary safety parameters.

Saroglitazar is the world's first approved dual PPAR-α/γ agonist.

**What are PPARs?**

Peroxisome Proliferator-Activated Receptors - PPAR are nuclear lipid activated transcription factors that regulate the expression of genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes. These receptors were identified in 1990 in rodents and named after their property of peroxisome proliferation. PPAR-α subtype is found in the liver, kidney, heart and muscles and is implicated in the uptake and oxidation of FAs and lipoprotein metabolism.

PPAR-γ subtype is mainly expressed in adipose tissue with lower expression detected in other tissues like spleen, intestine, pancreas, colon, kidney, skeletal muscle. PPAR-γ agonists increase insulin sensitivity and glucose disposal and prevent

loss of beta cells mass in the pancreas. PPAR-α agonists are used to lower TG levels.

**Mechanism of Action -**

PPAR-α activation causes up-regulation of genes invoved in lipid metabolism including fatty acid transport protein (FATP), AcylCoA synthase, carnitine palmitoyl transferase-CPT I and II, lipoprotein lipase (LPL) and down regulation of ApoC III. On the other hand, PPAR-γ activation leads to up-regulation of numerous genes involved in glucose and lipid metabolism including aP2, PEPCK, acylCoA synthase, LPL, FATP-1, & CD36, adiponectine etc.

This property of differential regulation of genes by different PPAR agonists is responsible for unique pharmacodynamics & safety profile of each PPAR agonist.

**Rationale of Developing Dual PPAR α/γ Agonist -**

By using dual PPAR agonist one can control both the lipid and glucose levels simultaneously. One recent study has demonstrated that combination therapy with PPAR-α & PPAR-γ agonist s, rosiglitazone & fenofibrate, results in normalization of TG & TC levels without increasing BMI & improves the atherogenic dyslipidemic profile in type 2 diabetic patients. Hence importance of controlling both lipids and glucose in metabolic syndrome gives rise to concept of identifying dual agonist which can activate both PPAR- α & PPAR- γ receptors.

**Physical and Chemical Properties -**

**Lipaglyn (Saroglitazar)** is the first glitazar compound that has been approved as a therapeutic agent. Structurally, saroglitazar is a non TZD and non fibrate molecule and belongs to aryl alkoxy propionic acid class. It has a strong PPAR- α effect and moderate PPAR- γ effect.

It is available as an oral tablet containing 4 mg of Saroglitazar.

***Chemical Name :*** (S)-a-ethoxy-4-[2[2-methyl-5-4[4-(methylthio)phenyl]-1H-pyrrol-1-yl]ethoxy] benzenepropanoic acid magnesium salt (2:1)

***Molecular Formula :*** $[C_{25}H_{28}NO_4S]_2Mg$

***Molecular weight :*** 900 atomic mass unit (amu)

**Indications and Usage-**

Lipaglyn is indicated for treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy.

**Dosage and Administration -**

The recommended dose of Lipaglyn is one tablet of 4 mg once a day orally.

**Contraindications -**

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

**Warnings and Precautions -**

Although clinical studies with Lipaglyn have not demonstrated any potential for myopathies or derangement of liver and / or renal functions, lipaglyn should be initiates with caution in patients with abnormal liver or renal functions, or history of myopathies. Also in patients with type 2 diabetes having cardiac disease with repeated congestive heart failure it should be initiated with caution.

**Adverse Events -**

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

**Use In specific Populations -**

The safety of lipaglyn has not been established in pregnant women, nursing mothers and pediatric patients as there is no adequate and well controlled study carried out in these populations.

**Summary -**

Cardiovascular disease is the leading cause of death in individuals with type 2 diabetes mellitus, accounting for 50% of all deaths[1]. Some clinical guidelines state that CV risk in patients with type 2 diabetes can be reduced by controlling dyslipidemia as well as hyperglycemia[2,3], but most patients still do

not achieve recommended goals for these risk factors[2,4]. A multifactorial intervention may be most appropriate for optimum reduction of CV risk[5].

The fibrates are agonists of PPAR-α, and their use in patients with type 2 diabetes leads to improvements in lipid profiles[2]. The PPAR-γ agonist pioglitazone is approved for glycemic control in type2 diabetes. Pioglitazone therapy has been associated with reduced risk of negative CV outcomes in type2 diabetes[6].

Clearly, an optimum PPAR agent with appropriate ratios of PPAR-α/γ agonist activity which can improve the safety profile, and , that provides both effective gycemic control and an improved lipid profile was the need of the hour.

Lipaglyn is a new, dual PPAR-α/γ agonist designed to optimize glycemic control and lipid benefits, and minimize PPAR-related adverse effects in the treatment of patients with type2 diabetes. Preclinical and clinical studies have shown favourable effects of lipaglyn on glycemic control, insulin sensitivity, and dyslipidemia along with very much acceptable safety and toxicity profile.

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Conflict of interest : None declared

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