

**SAROGLITAZAR: A NOVEL DUAL ACTING PEROXISOME PROLIFERATOR
ACTIVATED RECEPTOR (PPAR) IN DYSLIPIDEMIA ASSOCIATED WITH T2DM**Krishna¹, Ayesha Vaseem², Ravinder K. Sah^{1*} and Mazher Ali³¹Department of Pharmacology, Lady Hadrtinge Medical College, New Delhi, India- 110001.²Assistant Professor Department of Pharmacology, Deccan College of Medical Sciences, Hyderabad.³Consultant Care Hospital, Banjara Hills, Hyderabad.***Corresponding Author: Dr. Ravinder K. Sah**

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ABSTRACT

Diabetes is a common occurrence all over the world. It results in cardiovascular complications which lead to high mortality especially in developing countries. The development of drugs which control hyperglycemia as well as dyslipidemia in diabetes is an area of extensive research. Saroglitazar (Lipaglyn™) is the first dual PPAR agonist to hit the market, launched by an Indian pharmaceutical company in 2013. Lipaglyn™ is well absorbed orally and has a non-renal route of elimination. It is well tolerated, not associated with adverse effects like edema, weight gain, myopathies or derangement of liver and/or kidney functions, thus making it safe and efficacious. At a dose of 4 mg once daily, it reduces triglycerides and LDL cholesterol, it increases HDL cholesterol, and also shows a reduction in Fasting plasma glucose. Saroglitazar provides safe and effective alternative for the treatment of diabetic dyslipidemia. Though large studies are yet needed for long term safety.

KEYWORDS: Diabetes mellitus, Diabetic dyslipidemia, Saroglitazar.**INTRODUCTION**

Diabetes mellitus (DM) is a pandemic disease and increases the risk of heart disease and stroke. 52% of people with type 2 diabetes mellitus (T2DM) die of cardiovascular disease.^[1,2] The atherogenic dyslipidemia in diabetes (ADD) is characterized by high serum triglycerides (>150 mg/dl), high small dense lipoprotein (LDL) levels (>100mg/dl), low HDL levels postprandial lipemia.^[3, 4] Insulin resistance is a primary cause for ADD. Though statins are highly effective for cardiovascular disease (CVD) prevention in DM but a significant residual CV risk remains even after optimal statin therapy. Fibrates, niacin and omega-3 fatty acids are used in addition to statin for treatment of ADD (specifically hypertriglyceridemia). All these drugs have some limitations and they are far from being ideal companions of statins. The identification of agents that elevate HDL cholesterol in diabetic patients is an area of active interest. It has been well established that dyslipidaemia is a major CV risk factor and cause of mortality associated with T2DM^[5] thus all the major guidelines including the American Diabetes Association (ADA) recommends control of diabetic dyslipidaemia.

The role of peroxisome proliferator-activated receptor (PPAR) agonists in the treatment of type 2 diabetes mellitus patients to reduce the cardiovascular risk has long been an area of on-going medical research. The three PPAR receptors (PPAR- α , PPAR- β and PPAR- γ)

form a subfamily of nuclear receptors. They function as lipid sensors and regulate the expression of a large number of genes associated with metabolism. PPAR- α activators (fibrates, e.g. Clofibrate) are commonly used to treat dyslipidemia owing to their property to decrease triglyceride levels and increase HDL cholesterol levels. PPAR- γ is also expressed in a wide variety of tissues, with highest concentration being in adipose tissue^[6] PPAR- γ agonists are glitazone compounds e.g. Thiazolidinediones (TZD). They are approved for glycemic control in type 2 diabetes due to their reversal of lipid toxicity mechanisms and reduced secretions of inflammatory cytokines and chemokines, ultimately decreasing insulin resistance. In recent years combined PPAR- α and PPAR- γ therapeutic regimens (fibrates and glitazones) have been evaluated for treatment of type 2 diabetes mellitus. However, most of these compounds have been not been successful due to their profound side effects.^[7]

The Development of Dual PPAR Agonist

Zydus Cadila submitted a new drug application (NDA) for Lipaglyn™ or Saroglitazar (ZYH1) for approval to the Drug Controller General of India (DCGI) and it has been approved in June 2013 for treating diabetic dyslipidemia in T2DM not controlled by statins alone.

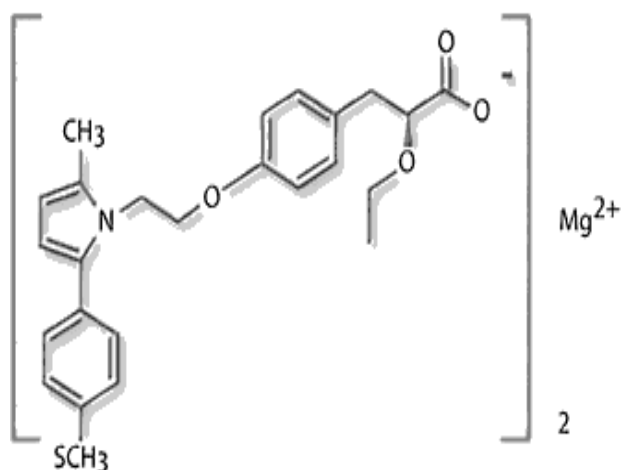


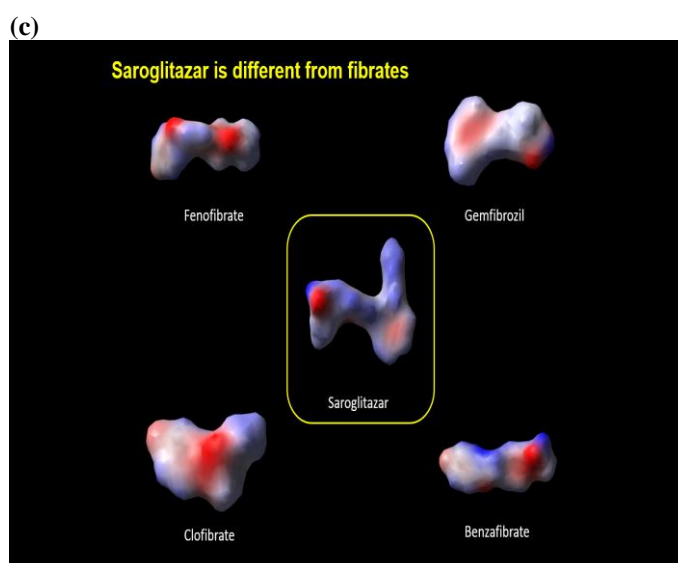
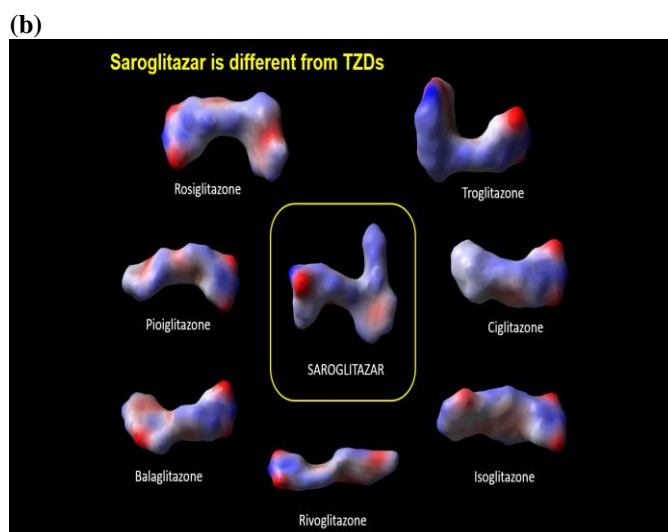
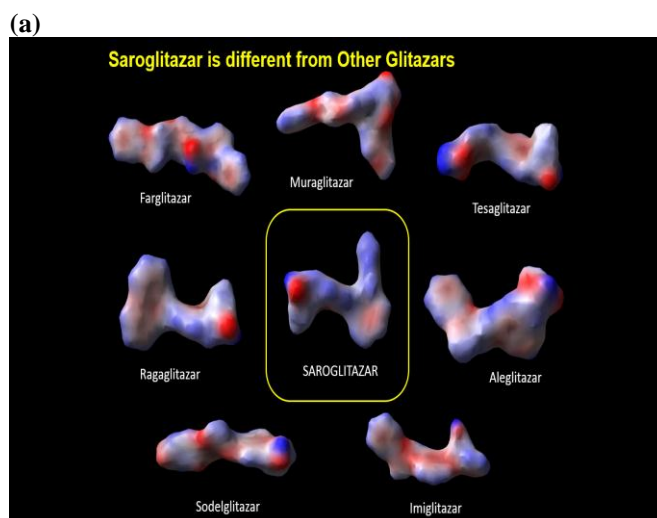
Figure-1: The structure of saroglitzar

Lipaglyn (Saroglitzar, [(*S*)- α -ethoxy-4-{2-[2-methyl-5-(4-methylthio)phenyl]-1H-pyrrol-1-yl]-ethoxy})-benzenepropanoic acid magnesium salt], is a compound from the glitazar group (figure-1). It is a dual PPAR agonist with predominant PPAR- α and moderate PPAR- γ activity. The nuclear receptor PPAR has subunits α and γ , which are activated by saroglitzar.^[8] PPAR- α receptors are present in fatty tissue, liver and muscles which when activated increase the synthesis of lipoprotein lipase leading to increased degradation of VLDL and reduce triglyceride levels, increases HDL levels and to some extent decrease LDL levels by increasing the uptake by liver. PPAR- γ receptor is present mostly in adipose tissue, muscle, liver and few other tissues. Activation of these receptors modulates the expression of insulin sensitive genes which enhances insulin action. They increase insulin mediated glucose transport into muscle and adipose tissue by increasing the synthesis of glucose transporters (GLUT4). They also increase glucose utilization by transcriptionally upregulating lipoprotein lipase, ApoA-1, ApoA-II and down regulating ApoC-III, an inhibitor of lipolysis. They reduce triglycerides mediated stimulation of fatty acid oxidation, increased LPL synthesis and reduced expression of ApoA-III and decreasing the VLDL levels. HDL -C level rises due to PPAR- α mediated stimulation of Apo-A-I and Apo A-II expression.^[9]

Fenofibrate a PPAR- α agonist is used to control dyslipidemia and Pioglitazone PPAR- γ agonist is used to control blood sugar levels. Saroglitzar is dual agonist has predominantly PPAR- α agonistic activity with optimal PPAR- γ agonistic activity.

Saroglitzar binds with PPAR- α strongly because of 4H bonding site than fenofibrate which binds to 2H bonding site. Hence Saroglitzar is more potent in activating PPAR- α than fenofibrate. Saroglitzar is completely different in structure and attributes from other glitazars. Saroglitzar lacks TZD ring, hence making it efficacious and safe.^[10]

Comparison of structure of saroglitzar with (a) Other Glitazars, (b) Thiazolidinediones (c) Fibrates:



Glitazars compounds were withdrawal in different phases in the trials^[11-17]

1. Tesaglitazar: first dual PPAR agonist was withdrawn in 2006.
2. Muraglitazar: It was approved by USFDA for clinical use as it was more effective than pioglitazone in reducing HbA1c but was withdrawn due to increased cardiovascular events in 2006.
3. Ragaglitazar: This was also withdrawn in 2004 as it was shown to cause bladder tumors.
4. Farglitazar: Clinical development ceased in 2003 because of weight gain, fluid retention and edema.
5. Imiglitazar: It showed hepatotoxicity and lacked efficacy in human trials.
6. Aleglitazar: This compound was withdrawn after phase III trial in 2013 because of increased incidence of bone fractures, heart failures and gastrointestinal bleed.^[17]

Most of these failed compounds had selectivity towards PPAR- γ receptors which has side effects like water retention, weight gain, heart failure and bone fractures.

Saroglitazar has high PPAR- α activity with moderate PPAR- γ activity hence achieves optimum anti-dyslipidaemic and anti-hyperglycaemic effects without any kind of toxic effects.^[12]

Preclinical Studies

Various toxicity studies showed saroglitazar safe and well tolerated and no toxic effect on myocardium, liver, kidney or muscle. It was found to possess an acceptable safety profile even at doses several times higher than the approved human dose of 4 mg. Doses as high as 3 mg/kg up to 125 mg/kg did not adversely affect mating/fertility behaviour in female rats and male rats respectively even at doses higher than efficacy dose. Saroglitazar was found to be non-genotoxic and non-teratogenic and passed 2 year carcinogenicity study.^[18]

Clinical Studies

Lipaglyn was approved based on the results obtained from phase I, Phase II and Phase III studies which were conducted for more than eight years. The studies evaluated the efficacy, safety, pharmacokinetics and pharmacodynamics of the drug.

Phase I study

Phase I trial was a Randomized, double-blind, placebo-controlled, single-centre study in 96 healthy human volunteers in single ascending oral doses of saroglitazar (0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64 and 128 mg). It also measured the effects of food and gender on the pharmacokinetics of 1 mg saroglitazar, the human equivalent efficacy dose derived from pre-clinical studies. Result showed that Saroglitazar was rapidly and well absorbed. Pharmacokinetics (C_{max} , AUC) was dose dependent and linear. The average terminal half-life was 5.6 h. Saroglitazar is chiefly eliminated in an unchanged form by the hepato-biliary route, without involving the

renal route. There was no effect of gender and food on the pharmacokinetics of saroglitazar, except for the terminal half-life, which was significantly shorter in females than in males. Single oral doses of saroglitazar up to 128 mg were well tolerated. No serious adverse events were reported. Mild to moderate intensity adverse effects like rash/itching, abdominal pain, nausea, cough, cold, headache, backache, body pain, calf pain, fever, malaise, giddiness, dyspepsia and diarrhoea were reported in 11 subjects.^[19]

Phase II study.

In a Prospective Randomized Efficacy and Safety of Saroglitazar (PRESS I-IV), each study was of 12 weeks duration with a total of 222 diabetic and nondiabetic participants. Saroglitazar (0.5 – 4 mg) was compared to fenofibrate, rosiglitazone and pioglitazone. Saroglitazar produced a dose-related (45%) reduction in triglyceride levels, which was higher than the decline in levels reported with fenofibrate (29-36%). Saroglitazar (4 mg) was also superior to pioglitazone 45 mg in reducing total cholesterol, LDL-C and VLDL-C while the effects on HDL-C, apolipoprotein A1, apolipoprotein B, FPG and HbA1c were comparable with both drugs.^[20]

Phase III trials**1) PRESS - V**

Saroglitazar (2 and 4mg) was compared with pioglitazone in patient of T2DM diabetes and dyslipidemia. In study Saroglitazar (4mg) had produced 45% decreased in TG with modest reduction in LDL-C, total cholesterol and mild increase in HDLC (3.8%) and also showed mild reduction in HbA1c (0.3%).

2) PRESS - VI

Saroglitazar (2mg - 4mg) used as add on to atorvastatin vs placebo in T2DM patients. At the 4mg dose Saroglitazar caused statistically significant improvement in TG and significant reduction in LDL-C, VLDL-C and also showed increase of 7.6% of HDL-C and 32% reduction in Apo B levels. Apo B levels were studied as it is helpful in management of patients with dyslipidemia. Saroglitazar (4mg) has the potential to achieve the target Apo B goal in dyslipidemia due to diabetes.

Saroglitazar has demonstrated a decrease in FPG of up to – 27.3mg/dL compared with baseline, which is significantly better than placebo. This decrease may be due to moderate PPAR- γ agonist activity. Decrease in level of glycosylated hemoglobin was not statistically significant, probably because of the short duration of the study.^[21] In this study saroglitazar has not shown potential for renal toxicity. This might be due to a non-renal route of excretion.^[22] During this study, there was no significant weight gain in subjects from the saroglitazar arm compared with baseline or the placebo arm. Although edema has been reported with aleglitazar, muraglitazar and other PPAR- γ agonists in earlier trials, there was no report of edema in the saroglitazar. There

were no changes in ECG and 2D-ECHO findings during the study period and also up to 24 weeks after the last dose of saroglitazar or placebo. No adverse cardiac event associated with saroglitazar was reported up to 24 weeks after the last dose of saroglitazar or placebo.^[11,15]

Drug Interactions

Saroglitazar did not show significant drug interaction clinical trials when given along with atorvastatin or metformin and / or sulfonylureas. No report of hypoglycaemia was reported, when given with one or more anti-diabetic drugs and also with insulin but blood glucose monitoring is advised. Concurrent administration with any other PPAR- α and/or PPAR- γ agonist is not recommended, as there may be drug-drug interactions but further studies are needed.^[23]

Ongoing research on Saroglitazar for Non-alcoholic steatohepatitis (NASH): Zydus has completed 52 week Phase III clinical trial of Lipaglyn™ in India to treat patients with biopsy proven NASH. Saroglitazar has demonstrated good efficacy in animal models of NASH, along with associated biomarkers. It has reduced hepatic steatosis, ballooning, inflammation and fibrosis in liver. A post-marketing Phase-IV study is currently underway in patients suffering from hypertriglyceridemia in India.^[24]

CONCLUSION

Saroglitazar (Lipaglyn) is dual PPAR (α and γ) agonist in its class and dual benefits in correcting dyslipidemia and hyperglycaemia in T2DM. It is structurally different from fenofibrate and pioglitazone and retains efficacy without any side effects of either. A non-renal route of elimination makes saroglitazar safe to be used in type 2 diabetes patients with renal compromise, however with caution. It was approved for and is being used in conjunction with statins for the management of ADD. Its final place in therapeutic armamentarium awaits the conduct and results of long term safety and cardiovascular outcome trials.

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