



Product  
Information



**Lipaglyn**<sup>™</sup>  
Saroglitazar

*Novel. Superior. Dual acting.*



**Zydu**s  
dedicated to *life*

**Zydu**s  
Discovery

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

## 1. COMPOSITION

Each uncoated tablet contains:

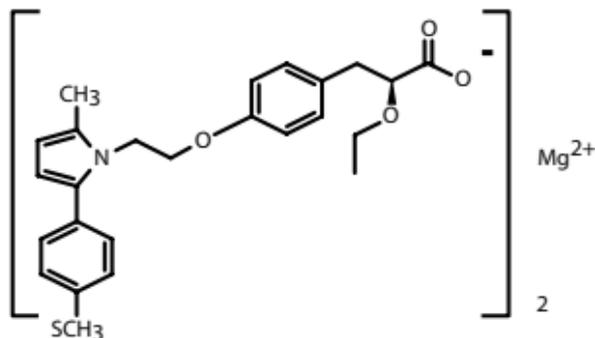
Saroglitazar 4 mg

Excipients q.s.

Inactive ingredients in the tablet are microcrystalline cellulose, lactose, magnesium oxide, povidone, talc, magnesium stearate, croscarmellose sodium and colloidal silicon dioxide.

## 2. DRUG DESCRIPTION

**LIPAGLYN™** (Saroglitazar) is a dual regulator that corrects both the lipid profile and the glycemic indices. It is available as an oral tablet containing 4 mg of Saroglitazar. The chemical name for Saroglitazar is Benzenepropanoic acid,  $\alpha$ -ethoxy-4-[2-[2-methyl-5-[4-(methylthio)phenyl]-1H-pyrrol-1-yl]ethoxy]-, magnesium salt (2:1), ( $\alpha$ S) - with the following structural formula:



The empirical formula of Saroglitazar is  $[C_{25}H_{28}NO_4S]_2Mg$  and the molecular mass is 900 g/mole.

## 3. INDICATIONS AND USAGE

**LIPAGLYN™** is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy. In clinical studies, **LIPAGLYN™** 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.

#### 4. DOSAGE AND ADMINISTRATION

The recommended dose of **LIPAGLYN™** is one tablet of 4 mg once a day.

#### 5. DOSAGE FORMS AND STRENGTHS

**LIPAGLYN™** is available as uncoated tablets for oral administration. Each uncoated tablet of **LIPAGLYN™** contains 4 mg of Saroglitazar.

#### 6. CONTRAINDICATIONS

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

#### 7. WARNINGS AND PRECAUTIONS

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

**LIPAGLYN™** has not been studied in patients with established New York Heart Association (NYHA) Class III or IV heart failure. **LIPAGLYN™** 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 during the clinical studies, no significant weight gain and edema was reported with **LIPAGLYN™**, patients who experience rapid increase in weight should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

#### 8. ADVERSE EVENTS

In two controlled phase III clinical studies of 12 to 24 weeks treatment duration with **LIPAGLYN™**, the most common adverse events (AEs  $\geq 2\%$ ) 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.

#### 9. 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 concentration of 10 $\mu$ M. Similarly, Saroglitazar did not show

any potential for CYP3A4 enzyme induction when tested up to 100  $\mu\text{M}$  concentration in luciferase based reporter assay in transiently transfected HepG2 cells. Although no clinical drug-drug interaction studies have been conducted with **LIPAGLYN™** so far, because the tested concentrations (10  $\mu\text{M}$  and 100  $\mu\text{M}$ ) are several times higher than the mean  $C_{\text{max}}$  of Saroglitazar, it can be inferred that **LIPAGLYN™** would not cause clinically significant drug-drug interactions related to the above evaluated CYPs.

## 10. USE IN SPECIFIC POPULATIONS

### 10.1 Pregnancy

Pregnancy: Category C

The safety of **LIPAGLYN™** 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 **LIPAGLYN™** treatment should contact their physicians. **LIPAGLYN™** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, effects of Saroglitazar on the embryo-fetal development were assessed in pregnant rats given repeated oral doses of 5, 25 and 125mg/kg/day. No maternal or fetal toxicity was noticed at 5 mg/kg, which is about 12-fold higher on body surface area basis than the maximum recommended human dose (MRHD) of **LIPAGLYN™** 4 mg. Saroglitazar was found to be non-teratogenic up to the highest dose of 125 mg/kg/day in rats.

In pregnant rabbits given repeated oral doses of 10, 50 and 200 mg/kg/day of Saroglitazar, no maternal toxicity was noticed up to 10 mg/kg and no fetal toxicity up to 50 mg/kg. Saroglitazar was found to be non-teratogenic up to the highest dose of 200 mg/kg/day in rabbits.

### 10.2 Nursing mothers

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

### 10.3 Pediatric use

Safety and efficacy of **LIPAGLYN™** in pediatric patients have not been established.

### 10.4 Geriatric use

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

## 11. OVERDOSE

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

## 12. CLINICAL PHARMACOLOGY

### 12.1 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. The pharmacological effects of Saroglitazar were extensively evaluated in various preclinical models. Saroglitazar showed both anti-dyslipidemic and anti-diabetic effects mainly mediated via activation of PPAR $\alpha$  and PPAR $\gamma$  respectively.

PPAR $\alpha$  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. PPAR $\alpha$  activation by Saroglitazar also induces an increase in the synthesis of apolipoproteins A-I, A-II and HDL-cholesterol.

Although Saroglitazar is predominantly a PPAR $\alpha$  agonist, it also causes activation of PPAR $\gamma$  and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Saroglitazar increases the expression of numerous PPAR $\gamma$ -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 glucose

utilization. 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.

## 12.2 Pharmacodynamics

### 12.2.1 Dyslipidemia with Type-II Diabetes Mellitus (T2DM):

The effects of LIPAGLYN™ 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 LIPAGLYN™ 4 mg or Pioglitazone (45 mg) for 24 weeks. The results are presented in Table 1 below:

<b>Table 1: Percent change in lipid and glycemic parameters following LIPAGLYN™ 4 mg treatment</b>		
<b>Time point</b>	<b>Week 12</b>	<b>Week 24</b>
<b>TG</b>	-46.1 ±5.6*#	-45.7 ±5.1*#
<b>Total cholesterol</b>	-7.3 ±3.6*	-6.9 ±3.8*#
<b>LDL cholesterol</b>	-0.4 ±6.5	-4.8 ±6.2*
<b>VLDL cholesterol</b>	-46.1 ±5.6*#	-46.1 ±5.2*#
<b>HDL cholesterol</b>	10.0 ±3.7*	4.6 ±3.9
<b>Apo A1</b>	0.7 ±4.8	2.2 ±8.2
<b>Apo B</b>	-11.9 ±5.4*	-9.8 ±5.4*
<b>FPG<sup>^</sup></b>	-15.2 ±3.5*	-11.5 ±5.8*
<b>HbA1c</b>	-0.3 ±0.1*	-0.3 ±0.1*

All values are presented as Least Square Mean (LSM) ± Standard Error (SE) of Per Protocol (PP) population,  
 \*Statistically significant change as compared to the baseline  
 #Statistically significant change as compared to Pioglitazone,  
 ^ FPG values presented as Mean ± SE of PP population

When compared to Pioglitazone, **LIPAGLYN™** 4 mg achieved the ATP III goal in more subjects as depicted in Table 2.

**Table 2: Percentage of patients achieving ATP III Goal following LIPAGLYN™ 4 mg treatment as compared to Pioglitazone**

<b>ATP Goal*</b>	<b>LIPAGLYN™ 4 mg (%)</b>	<b>Pioglitazone 45 mg (%)</b>
Not achieved even one criteria	29.4	50.0
Achieved one criteria	26.5	22.7
Achieved two criteria	35.3	27.3
Achieved all three criteria	8.8	0.0

\* ATP – Adult Treatment Panel III of US National Cholesterol Educational Program, 2002-2003,  
Male : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 40 mg/dl,  
Female : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 50 mg/dl

In another study, the effect of **LIPAGLYN™** at 4 mg per day was assessed in diabetic patients with hypertriglyceridemia not controlled with Atorvastatin 10 mg therapy. The patients were treated with **LIPAGLYN™** 4 mg or placebo for 12 weeks along with Atorvastatin 10 mg. The results are presented in Table 3 below:

<b>Table 3: Percent change in lipid and glycemic parameters following LIPAGLYN™ 4 mg treatment</b>		
<b>Time point</b>	<b>Week 6</b>	<b>Week 12</b>
<b>TG</b>	-46.4 ±3.1*#	-47.2 ±3.2*#
<b>Total cholesterol</b>	-23.6 ±1.9*	-25.8 ±1.8*#
<b>LDL cholesterol</b>	-28.1 ±2.5*	-30.7 ±2.4*#
<b>VLDL cholesterol</b>	-45.1 ±3.3*#	-46.5 ±3.2*#
<b>HDL cholesterol</b>	8.3 ±2.8	8.1 ±2.5#
<b>ApoA1</b>	8.1 ±3.2	9.2 ±4.5
<b>Apo B</b>	-29.1 ±2.4*	-32.1 ±2.3*#
<b>FPG</b>	-14.9 ±3.7*#	-10.5 ±4.2*#
All values are presented as LSM ± SE of PP population, *Statistically significant change as compared to the baseline, #Statistically significant change as compared to the placebo		

In combination with Atorvastatin, **LIPAGLYN™** achieved the ATP-III goal in more subjects than Atorvastatin alone; hence demonstrating better cardiovascular risk reduction. (Table 4)

**Table 4: Percentage of patients achieving ATP Goal following LIPAGLYN™ 4 mg treatment as compared to placebo in combination with Atorvastatin**

ATP Goal *	LIPAGLYN™ 4 mg + Atorvastatin 10 mg (%)	Placebo + Atorvastatin 10 mg (%)
Not achieved even one criteria	10.3#	30.1
Achieved one criteria	30.8	38.6
Achieved two criteria	43.6	24.1
Achieved all three criteria	15.4	6.0

\* Male : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 40 mg/dl  
 Female : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 50 mg/dl  
 # significantly different from placebo + Atorvastatin 10 mg

**LIPAGLYN™** has also shown a decrease in TG, LDL, VLDL, non-HDL cholesterol and TC with an increase in HDL in non-diabetic patients.

There was no incidence of hypoglycemia reported during Phase I-III trials in both diabetic and non-diabetic subjects.

### 12.3 Human Pharmacokinetics

The single dose pharmacokinetics of **LIPAGLYN™** was assessed across the dose range of 0.125 to 128 mg.

### 12.3.1 Absorption

Following oral administration in healthy volunteers, peak plasma levels of Saroglitazar occurred at approximately 1 hour post-dosing in both the genders.

Maximum plasma concentration ( $C_{max}$ ) and area under the curve ( $AUC_{0-\infty}$ ) of Saroglitazar increased proportionally with the administered single doses of 0.125 mg - 128 mg per day. After single oral dose of **LIPAGLYN™** 4 mg in healthy volunteers,  $C_{max}$  of  $337.1 \pm 91.0$  ng/ml (Mean  $\pm$  SD, n=6) was observed.

Pooled analysis of male and female healthy volunteers showed no gender effect or food effect on pharmacokinetics of Saroglitazar.

### 12.3.2 Distribution

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

### 12.3.3 Metabolism

In healthy volunteers, **LIPAGLYN™** 4 mg has an apparent oral clearance,  $CL/F$ , calculated to be  $4.8 \pm 0.93$  L/hr.

*In vitro* studies using pooled human liver microsomes showed that Saroglitazar is metabolically stable.

Following **LIPAGLYN™** 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.

### 12.3.4 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.

## 13. NON CLINICAL TOXICOLOGY

### 13.1 Acute and Chronic Toxicity Studies

Various acute and chronic toxicity studies were performed in mice, rats and dogs up to a duration of 12 months. In acute dose studies, the maximum tolerated dose (MTD) in Swiss albino mice was 500 mg/kg, and in Wistar rat it was 1200 mg/

kg. Safety pharmacology studies did not reveal any adverse changes in CNS, CVS, respiratory and gastrointestinal parameters. In repeat dose toxicity studies, Saroglitazar was shown to have an acceptable safety profile at doses several-fold higher than the approved human doses. At high doses, the toxic effects observed were mainly the exaggerated pharmacological effects mediated by PPAR mechanisms.

### 13.2 Impairment of Fertility

Saroglitazar did not show any adverse effects on mating or fertility in male rats up to 125 mg/kg (more than 250 times the approved human dose on body surface area basis). In female rats no adverse effects on fertility were observed up to 3 mg/kg (7 times the approved human dose on body surface area basis). Saroglitazar altered the estrus cyclicity and litter indices at 15 mg/kg which is 35 times the human recommended dose.

During pre- and post-natal developmental study in rats, Saroglitazar did not show any adverse effects on reproductive performance and lactating indices up to 1 mg/kg which is more than the human therapeutic dose.

### 13.3 Carcinogenicity

Two-year carcinogenicity study of Saroglitazar was conducted in Wistar rats. No potential carcinogenic concern for humans was identified, which was further confirmed by a mechanistic study in non-human primates employing molecular biomarkers.

### 13.4 Mutagenicity

Saroglitazar was found to be non-mutagenic and non-genotoxic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity test, chromosomal aberration assay using the peripheral human blood lymphocytes and the mouse micronucleus assay.

## 14. HOW SUPPLIED

**LIPAGLYN™** is supplied as uncoated round biconvex tablets with "4" written on one side and plain on the other side. Available as 4 mg strength.

**LIPAGLYN™** tablets are supplied as 10 tablets in an alu-alu blister. Each blister is packed in a mono-carton.

## 15. STORAGE AND HANDLING INSTRUCTIONS

Store below 25°C and in dry place. Protect from light. Keep out of reach of children.

## 16. MANUFACTURED BY

**CADILA HEALTHCARE LIMITED**, Sarkhej-Bavla National Highway No. 8A,  
Moraiya, Tal.: Sanand, Dist.: Ahmedabad - 382 210, Gujarat.

## 17. MARKETED BY

**Zydus  
Discovery**

**Zydus**  
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<sup>TM</sup> Trademark applied for.

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For more detail visit : [www.lipaglyn.com](http://www.lipaglyn.com)

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