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

VORXAR

1. Generic Name

Saroglitazar Tablets

2. Qualitative and quantitative Composition:

Each uncoated tablet contains:

Saroglitazar 4 mg

Excipients q.s.

Colour: Red Oxide of Iron

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

3. Dosage form and strength

Dosage form: Saroglitazar is available as uncoated tablets for oral administration.

Strength: Each uncoated tablet of Saroglitazar contains 4 mg Saroglitazar

4. Clinical particulars

4.1 Therapeutic indication

Saroglitazar is indicated in adults for the treatment of

- Noncirrhotic Non-Alcoholic Steatohepatitis (NASH)
- Patients of Non-alcoholic Fatty liver Disease (NAFLD) with comorbidities (Either Obesity, Type 2 Diabetes Mellitus, Dyslipidemia or Metabolic Syndrome)

4.2 Posology and method of administration

Advise the patient to take Saroglitazar tablet once daily.

For, NASH and NAFLD with comorbidities (Either Obesity, Type2DiabetesMellitus, Dyslipidemia or Metabolic Syndrome)

- The recommended dose of Saroglitazar is one tablet of 4 mg once daily.
- Saroglitazar can be taken without regards to food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

4.5 Drugs interactions

In vitro studies using recombinant human Cytochrome p.450 (CYP) isozymes indicate that Saroglitazar does not significantly inhibit CYP1A2, 2C9, 2C19, 206 and 3M at concentration of 10µM. Similarly, Saroglitazar did not show any Potential for CYP3A4 enzyme induction when tested up to100 µM concentration in luciferase based reporter assay in transiently transfected HepG2 cells. Although no clinical drug-drug interaction studies have been conducted with

Sarog1itazar 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.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

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 foetus. In animal studies, effects of Saroglitazar on the embryo-fetal development were assessed in pregnant rats given repeated oral doses of 5, 25 and 125 mg/kg/day. No maternal or fetal toxicity was noticed at 5 mg/kg, which is about 12-lold higher on body surface area basis than the maximum recommended human dose (MRHD) of Saroglitazar 4 mg. Saroglitazar was found to be nonteratogenic up to the highest dose of 125 mg/kg day in rats. In pregnant rabbits given repeated oral doses of 10, 50 and 200mg/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.

Nursing mothers

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

Pediatric use

Safety and efficacy of Sarog1itazar in pediatric patients have not been established.

Geriatric use

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

4.7 Effects on ability to drive and use machines

It does not have any side effects upon driving and use of machines.

4.8 Undesirable effects

In a phase III randomized double-blind study of 52 weeks duration in NASH patients, The most frequently reported TEAEs (in5%of patients) were: flatulence 5 (7.4%),dyspepsia 6 (8.8%), abdominal distension 4 (5.9%) and asthenia 4 (5.9%) in Saroglitazar 4 mg group and flatulence 6 (17.S°/4), pyrexia 3 (8.8%), upper abdominal pain 3 (8.8%) and abdominal pain, constipation, asthenia, gastrointestinal motility disorder, cough and pruritus each of 2 (5.9%) in Placebo group.

In a phase III randomized double-blind study of 24 weeks duration in NAFLD patients. The most frequently reported TEAEs (in ≥ 2%of subjects) were: upper abdominal pain 1 (2.9%) in Saroglitazar 4 mg group and abdominal discomfort, constipation, nausea, vomiting, hypochromic anaemia, furuncle and pruritus each of 1 (2.9%) in Placebo group.

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.

Reporting of side effects

If you experience any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact.

Torrent Pharma available at:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 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, inducting monitoring of vital signs and observation of clinical status.

5 Pharmacological properties

5.1 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 1ipoprotein 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 PPARα and PPARy respectively.

PPARα activation by Saroglitazar increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of triglycerides (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-111 (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 PPARy and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Saroglitazar increases the expression of numerous PPARy- 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 Sarog1itazar were observed in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues.

5.2 Pharmacodynamic properties

Pharmacodynamic effects

Clinical development program of Saroglitazar has completed one phase 2 study and one phase 3 study in NASH patients and one phase 3 study in NAFLD patients (See below for more details).

Nonalcoholic Steatohepatitis

Phase II Study

Saroglitazar magnesium was evaluated during the phase II development program in NASH patients. The phase II study in NASH patients was a prospective, multi-center, open-label, single arm study to evaluate the safety and efficacy of 4 mg of Saroglitazar in NASH. A total of 32 subjects were enrolled in this study. The total duration of the study was 12 weeks. The NASH phase II study observed the following results:

Primary endpoint:

- The mean (± SD) change in ALT (UJL) from baseline of the Saroglitazar 4 mg at Week 6 and Week 12 were: -0.79±38.76 U/L and -49.30 ± 38.47 U/L, respectively. Saroglitazar 4 mg treatment showed statistically significant reduction in the ALT levels from baseline in ITT and PP population at Week 6 and Week 12 (p-value <0.0001).

Secondary Endpoints:

- Sustained reduction in ALT level was observed in 72.41% and 78.57% of patients at Week 6 and Week 12, respectively, in the ITT population.
- Sustained reduction in ALT level was observed in 63.16% and 78.95% of patients at Week 6 and Week 12, respectively, in the PP population
- The change in C peptide level was statistically non-significant after Saroglitazar 4 mg treatment at 6 and 12 weeks in the ITT population.
- In PP analysis, there was statistically non-significant change in the C peptide levels in Saroglitazar 4 mg at 6 weeks but a statistically significant change at 12 weeks. (p-value < 0.0349)
- There was statistically significant decrease in HOMA- beta cell function in Saroglitazar 4 mg at week 12 as compared to baseline in the ITT and PP population (p-value 0.0368 and 0.0158 respectively).
- There was statistically significant decrease in HOMA Insulin resistance in Saroglitazar 4 mg at week 12 as compared to baseline in the ITT and PP population (p-value 0.0216 and0.0167 respectively).
- In both, PP and ITT population, the TG values were significantly reduced from baseline to week 6 and week 12 in patients with baseline TG ≥ 150mg/dl.
- Similarly, the TG values were significantly reduced from baseline to week 6 and week 12 in patients with baseline TG < 150mg/dL in PP and ITT population.

There were 32 subjects exposed to Saroglitazar 4 mg, of which 29 subjects received the study drug for entire 12 weeks period. Three subjects dropped out or withdrew prematurely and did not receive the study drug for the entire study duration. All subjects were analysed for safety. No SAEs or deaths or significant AEs were reported during this study. The results are presented in Table 1 and Table 2 below:

Table 1: Analysis of change from baseline in ALT (U/L) by visit-wise (ITT Population)

Week		**Saroglitazar 4 mg (N=32)**
Week 6	n	29
	Mean ± SD	-43.79±38.76
	Median (Range)	-39.76 (9.72, -188.49)
	p-va!ue	<.0001
Week 12	n	28
	Mean ± SD	-49.30±38.47
	Median (Range)	-44.08 (-2.28, -159.37)
	p-value	<.0001

Abbreviations: mg/dL = milligram per deciliter; N = number of subjects in the treatment group; n =number of subjects with non missing value in the treatment group at the corresponding visit. Note: p-value are calculated from Student's t Test

Table 2: Analysis of change from baseline in ALT (U/L) by visit-wise (PP Population)

Week		Saroglitazar 4 mg
Week6	n	19
	Mean ± SD	-43.07±28.60
	Median (Range)	-42.87 (-6.70, -87.74)
	p-va1ue	<.0001
Week 12	n	19
	Mean ± SD	-51.49±32.79
	Median (Range)	-46.02 (·12.00, -147.43)
	p-value	<.0001
Abbreviations: mg/dL= milligram per deciliter; N = number of subjects in the treatment group; n = number of subjects with non missing value in the treatment group at the corresponding visit. Note: p-value are calculated from Student's t Test		

Phase III Study

Saroglitazar magnesium was evaluated during the phase III development program in NASH patients. The phase III study in NASH patients was a prospective, multicentre, double-blind, randomized trial of Saroglitazar 4 mg versus placebo in patients with Non-Alcoholic Steatohepatitis. A total of 102 patients were enrolled in this study. The total duration of the study was 52 weeks. The primary efficacy endpoint was proportion of patients with decrease in NAS ≥2 spread across at least 2 of the NAS components with no worsening of fibrosis with Saroglitazar 4 mg compared to placebo at Week 52. The NASH phase Ill study results concluded the proportion of patients who achieved the primary endpoint at week 52 was significantly higher in saroglitazar 4 mg arm (52.3%) compared to placebo (23.5%) (p value =0.0427). The primary endpoint of the study was met Saroglitazar 4 mg significantly reduced mean score of steatosis, lobular inflammation, and hepatocyte ballooning at Week 52. Saroglitazar 4 mg significantly reduced liver biochemical parameters such as AST, ALT, ALP, GGT at Week 52. Saroglitazar 4 mg also significantly reduced lipid parameters such as TG, LDL, sdLDL, VLDL, total cholesterol, non-HDL-C and apolipoprotein B at Week 52. Overall, Saroglitazar 4 mg improved liver histology, liver parameters and lipid parameters over a period of 52 weeks.

No deaths were reported during the study. No subject discontinued the study due to SAEs. Three SAEs (severe abdominal pain, bladder outlet obstruction, pain at biopsy site) were reported in the Saroglitazar 4 mg group but none was related to Saroglitazar treatment. The most frequently reported TEAEs (in ≥ 5% of patients) were: flatulence 5 (7.4%), dyspepsia 6 (8.8%), abdominal distension 4 (5.9%) and asthenia 4 (5.9%) in Saroglitazar 4 mg group and flatulence 6 (17.6%), pyrexia 3 (8.8%), upper abdominal pain 3 (8.8%) and abdominal pain, constipation, asthenia, gastrointestinal motility disorder, cough and pruritus each of 2 (5.9%) in Placebo group. Overall, treatment with Saroglitazar 4 mg for 52 weeks was safe and well tolerated.

The results are presented in Table 3 below:

Table 3: Proportion of Patients Achieving Primary Endpoint of Decrease in NAS ≥2 Spread Across at Least 2 of the NAS Components with no Worsening of Fibrosis at Week 52

	Saroglitazar 4 mg (N=44)	Placebo (N=17)	Difference (%) (95%CI)[+]	P-value[a]
Patients achieving primary endpoint of decrease in NAS ≥2 spread across at least 2 of the NAS components with no worsening of fibrosis, n (%)	23 (52.3)	4 (23.5)	28.7 (-2.08, 50.5)	0.0427

[+]Confidence intervals are based on the large-sample approximation method for binary data

[a] using chi-square test

N = Total Number of patients in each treatment group with available liver biopsy data

n = number of patients with the response category.

Non-a1cohollc Fatty Liver Disease (NAFLD)

Phase III Study

Saroglitazar magnesium was evaluated during the phase III development program in NAFLD patients. The phase III study in NAFLD patients was a prospective, multicenter, randomized, double-blind study. A total of 68 patients were enrolled in this study. The study was conducted over a period of up to 26 weeks. The NAFLD phase III study results concluded that the within group mean change in liver fat content from baseline of the Saroglitazar 4 mg and Placebo treatment groups at Week 24 were: •2.83 :t 6.30 and -1.78 ± 6.27 respectively. Compared with placebo, Saroglitazar was associated with a clinically meaningful reduction in liver fat content (13.79 % reduction in the Saroglitazar 4 mg vs 3.96% reduction in the placebo group) at Week 24.

The within group mean change in liver stiffness from baseline of the Saroglitazar 4 mg and Placebo treatment groups at Week 12 and 24 were: - 0.21 ± 2.45 for Saroglitazar 4 mg and 0.41 ± 3.98 for Placebo at Week 12 and -0.85 ± 3.09 for Saroglitazar 4 mg and -0.68 ± 5.26 for placebo at Week 24. Compared with placebo, Saroglitazar was associated with a clinically meaningful reduction in liver stiffness (3.76 % reduction in the Saroglitazar 4 mg vs 1.96% increase in liver stiffness in the Placebo group) at Week 24.

The within group mean change in ALT from baseline of the Saroglitazar 4 mg and Placebo treatment groups at Week 12 and 24 were: -20.20 ± 28.97 U/L for Saroglitazar 4 mg and -12.45 ± 24.50 U/L for Placebo at Week 12 and -20.53 ± 27.38 U/L for Saroglitazar 4 mg and -16.45 ± 24.46 U/L for placebo at Week24. Compared with placebo, Saroglitazar was associated with a clinically meaningful reduction in ALT (21.04% reduction in the Saroglitazar 4 mg vs 10.02% reduction in the placebo group at Week 12 and 27.31% reduction in the Saroglitazar 4 mg vs 14.29% reduction in the placebo group at Week 24) at Week 12 and 24.

No deaths and SAEs were reported during the study. The most frequently reported TEAEs (in ≥ 2% of subjects) were: upper abdominal pain 1 (2.9%) in Saroglitazar 4 mg group and abdominal discomfort, constipation, nausea, vomiting, hypochromic anaemia, furuncle and pruritus each of 1 (2.9%) in Placebo group.

Overall, Saroglitazar 4 mg reduced liver fat content, liver stiffness and ALT levels over a period of 24 weeks. The results are presented in Table 4, Table 5 and Table 6 below:

Table 4: Descriptive Summary of Liver Fat Content by Visit (Per-Protocol Population)

Visit	Saroglitazar 4 mg (N=31)			Placebo (N=29)		
	Measured Value	**Change from Baseline**	**% Change from Baseline**	**Measured Value**	**Change from Baseline**	**%Change from Baseline**
Baseline						
n	**31**			**29**		
Mean ± SD	18.03± 4.58			19.69 ±7.41		
Median	17.10			18.40		
(Min, Max)	(11.17, 29.13)			(10.11, 40.37)		
Week 24						
n	**31**	**31**	**31**	**29**	**29**	**29**
Mean ± SD	15.20±6.38	-2.83 ±6.30	-13.79 ± 33.99	17.92 ±6.51	-1.78 ± 6.27	-3.96 ± 33.41
Median	15.67	-1.84	-10.13	17.60	-1.56	-8.86
(Min, Max)	(3.14, 30.03)	(-20.37, 5.87)	(-76.58, 51.57)	(8.35, 37.00)	(-23.80, 12.70)	(-58.95, 104.10)
p-value*		0.018	0.031		0.138	0.529

N = number of subjects in the treatment group; n = number of subjects with the available data; Change=visit value – baseline value; % change = (visit value – baseline value)*100/baseline value; *Using paired t-test; Baseline = Screening visit

Table 5: Descriptive Summary of Liver Stiffness by Visit (Per-Protocol Population)

Visit	Saroglitazar 4 mg (N=31)			Placebo (N=29)		
	Measured Value	**Change from Baseline**	**% Change from Baseline**	**Measured Value**	**Change from Baseline**	**%Change from Baseline**
Baseline						
n	**31**			**29**		
Mean ± SD	8.73± 3.37			9.36 ±6.13		
Median	8.10			7.70		
(Min, Max)	(4.00, 16.30)			(4.70, 35.00)		
Week 12						
n	**31**	**31**	**31**	**29**	**29**	**29**
Mean ± SD	8.52±3.20	-0.21 ±2.45	-2.44 ± 29.70	9.77 ±6.63	0.41 ± 3.98	6.81 ± 45.68
Median	7.60	-0.10	-1.40	7.80	-0.10	-0.10
(Min, Max)	(4.10, 17.00)	(-6.30, 3.80)	(-42.57, 72.09)	(4.00, 30.00)	(-5.00, 17.80)	(-50.62, 202.27)
p-value*		0.643	0.651		0.583	0.429
Week 24						
n	**31**	**31**	**31**	**29**	**29**	**29**
Mean ± SD	7.88 ± 2.84	-0.85 ± 3.09	-3.76 ± 28.04	8.68 ± 4.24	-0.68 ± 5.26	1.96 ± 39.41
Median	7.50	-0.20	-2.20	6.90	-0.60	-4.52
(Min, Max)	(3.50, 17.20)	(-9.20, 3.70)	(-62.16, 40.48)	(4.10, 20.00)	(-23.70, 10.80)	(-67.71, 122.73)
p-value*		0.137	0.461		0.490	0.791

N = number of subjects in the treatment group; n = number of subjects with the available data; Change=visit value – baseline value; % change = (visit value – baseline value)*100/baseline value; *Using paired t-test

Table 6: Descriptive Summary of Serum Alanine Aminotransferase by Visit(Per-Protocol Population)

Visit	Saroglitazar 4 mg (N=31)			Placebo (N=29)		
	Measured Value	**Change from Baseline**	**% Change from Baseline**	**Measured Value**	**Change from Baseline**	**%Change from Baseline**
Baseline						
n	31			29		
Mean ± SD	62.36± 30.47			64.94 ±30.05		

Median	59.50			71.20		
(Min, Max)	(13.30, 137.90)			(14.80, 140.60)		
Week 12						
n	31	31	31	29	29	29
Mean ± SD	42.16±21.21	-20.20 ±28.97	-21.04 ± 55.44	52.50 ±28.76	-12.45 ± 24.50	-10.02 ± 40.71
Median	37.60	-17.20	-33.81	44.60	-7.20	-16.91
(Min, Max)	(9.20, 93.20)	(-69.20, 65.00)	(-78.08, 230.50)	(11.30, 153.90)	(-73.40, 27.60)	(-86.66, 89.02)
p-value*		<0.001	0.043		0.011	0.196
Week 24						
n	31	31	31	29	29	29
Mean ± SD	41.83 ± 26.27	-20.53 ± 27.38	-27.31 ± 35.49	48.50 ± 19.70	-16.45 ± 24.46	-14.29 ± 40.97
Median	35.00	-16.30	-30.94	47.40	-20.60	-26.60
(Min, Max)	(9.60, 116.30)	(-68.90, 37.60)	(-73.14, 59.03)	(17.30, 94.40)	(-68.80, 37.40)	(-59.21, 89.64)
p-value*		<0.001	<0.001		0.001	0.071
N = number of subjects in the treatment group; n = number of subjects with the available data; Change=visit value – baseline value; % change = (visit value - baseline value)*100/baseline value; *Using paired t-test						

5.3 Pharmacokinetic properties

The single dose pharmacokinetics of Saroglitazar was assessed across the dose range of 0.125 to128mg.

Absorption

Following oral administration in healthy volunteers, peak plasma levels of Saroglitazar occurred at approximately 1 hour post-dosing in both the genders. 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 Saroglitazar 2 mg and 4 mg in healthy volunteers, C_{max} of 223.2 ± 27.4 ng/mL (Mean ± SD, n=6) and 337.1 ± 91.0 ng/mL (Mean ± SD, n=6) were observed, respectively.

Two open-label, single-treatment, single-period, single dose pharmacokinetic study of Saroglitazar 2 mg and 4 mg were conducted in healthy adult males under fasting condition. After single oral dose of Saroglitazar 2 mg, mean C_{max} and AUC_{0-t} of saroglitazar were 138.261 ng/mL and 426.140 hr*ng/mL, respectively. After single oral dose of Saroglitazar 4 mg, mean C_{max} and AUC_{0-t} of saroglitazar were 305.852 ng/mL and 945.203 hr*ng/mL, respectively.

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

Distribution

The mean apparent oral volume of distribution (Vd/F) of Saroglitazar following single-dose administration of Saroglitazar 2 mg and 4 mg were 57.26 ±25.68 L and 20.14 ± 6.92 L, respectively. In vitro Saroglitazar is extensively protein bound (~96%) in human plasma. Multiple-dose studies in humans have shown that Saroglitazar does not undergo accumulation on repeat dosing once daily for 10 days. In open-label, single-treatment, single-period pharmacokinetic study, after single oral dose of Saroglitazar

2 mg, mean elimination half-life of saroglitazar was 6.267 hours and mean volume of distribution was 44.126 L. In open-label, single-treatment, single-period pharmacokinetic study, after single oral dose of Saroglitazar 4 mg, mean elimination half-life of saroglitazar was 6.069 hours and mean volume of distribution was 39.191 L.

Metabolism

In healthy volunteers, Saroglitazar 2 mg and 4 mg has an apparent oral clearance, CL/F, calculated to be 2.8 ± 0.69 L/ hr and 4.8 ± 0.93 L/hr, respectively. 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. In open-label, single-treatment. Single-period pharmacokinetic study, after single oral dose of Saroglitazar 2 mg and 4 mg, mean apparent oral clearance rate of saroglitazar was 5.142 L/hr and 4.667 L/hr, respectively.

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.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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 (MTO) 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.

Impairment of Fertility

Saroglitazar did not show any adverse effects on mating or fertility in male rats up to125mg/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.

Carcinogenicity

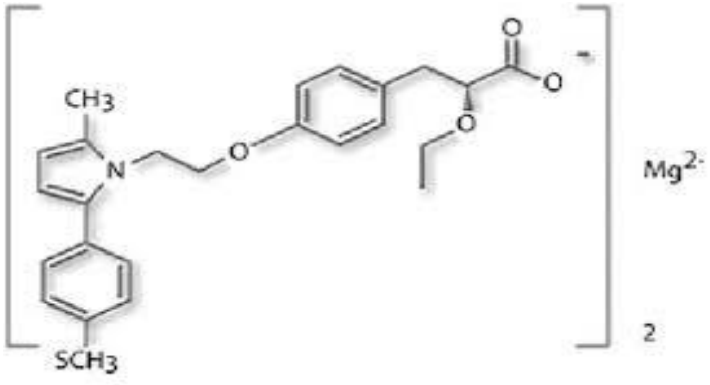
Two-year carcinogenicity study of Saroglitazar was conducted in Wistar rats. No potential carcinogenic concern for humans was identified, which was further confirmed by a mechanistic study in non-human primates employing molecular biomarkers.

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.

7 Description

Saroglitazar is a dual regulator that corrects both the lipid profile and the glycemic indices. The chemical name for Saroglitazar is Benzenepropanoic acid, α-ethoxy-4-[2-(2-methy1-5-[4-(methylthio) phenyl]-1H-pyrrol-1-yl] ethoxy]-, magnesium salt (2:1), (αS) - with the following structural formula in Figure 1:



The empirical formula of Saroglitazar magnesium is $[C_{25}H_{28}NO_4S]_2$ Mg and the molecular mass is 901.4 g/mol.

8 Pharmaceutical particulars

8.1 Incompatibilities

There is no known incompatibilities of Saroglitazar Tablets.

8.2 Shelf-life

30 months

8.3 Packaging information

Saroglitazar tablets are supplied as Light pink top ink colored, mottled surface, triangle shaped, beveled convex uncoated tablets, debossed with 4 at upper side and plain at lower side, available as 4 mg strength. Saroglitazar tablets are supplied as 10's tablets in Alu.-Alu blister.

8.4 Storage and handing instructions

Store below 25ºC in dry place. Protect from light.
Keep out of reach of children.

9 Patient Counselling Information

VORXAR

(Saroglitazar Tablets)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

What is in this leaflet?

9.1 What VORXAR is and what it is used for

Vorxar is contain Saroglitazar is available as uncoated tablets for oral administration. Each uncoated tablet of Saroglitazar contains 4 mg Saroglitazar.

Saroglitazar is indicated in adults for the treatment of

• Non cirrhotic Non-Alcoholic Steatohepatitis (NASH)

• Patients of Non-alcoholic Fatty liver Disease (NAFLD) with comorbidities (Either Obesity, Type 2 Diabetes Mellitus, Dyslipidemia or Metabolic Syndrome)

9.2 What you need to know before you take VORXAR

Vorxar 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.

9.3 How to take VORXAR

Advise the patient to take Vorxar tablet once daily.

For, NASH and NAFLD with comorbidities (Either Obesity, Type 2 Diabetes Mellitus, Dyslipidemia or Metabolic Syndrome)

• The recommended dose of Saroglitazar is one tablet of 4 mg once daily.

• Saroglitazar can be taken without regards to food.

9.4 Possible side effects

In a phase III randomized double-blind study of 52 weeks duration in NASH patients, The most frequently reported TEAEs (in 5% of patients) were: flatulence 5 (7.4%),dyspepsia 6 (8.8%), abdominal distension 4 (5.9%) and asthenia 4 (5.9%) in Saroglitazar 4 mg group and flatulence 6 (17.S°/4), pyrexia 3 (8.8%), upper abdominal pain 3 (8.8%) and abdominal pain, constipation, asthenia, gastrointestinal motility disorder, cough and pruritus each of 2 (5.9%) in Placebo group.

In a phase III randomized double-blind study of 24 weeks duration in NAFLD patients. The most frequently reported TEAEs (in ≥ 2% of subjects) were: upper abdominal pain 1 (2.9%) in Saroglitazar 4 mg group and abdominal discomfort, constipation, nausea, vomiting, hypochromic anaemia, furuncle and pruritus each of 1 (2.9%) in Placebo group.

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.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of

Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store VORXAR

Store below 25ºC in dry place. Protect from light.

Keep out of reach of children.

9.6 Contents of the pack and other information

Saroglitazar tablets are supplied as 10's tablets in Alu.-Alu blister.

10 Details of manufacturer

Manufactured by: Zydus Lifesciences Ltd.

Survey No. 417, 419 and 420, Sarkhej Bavla

National Highway No. 8A, Village - Moraiya,

Tal-Sanand, Dist-Ahmedabad - 382 210

11 Details of permission or licence number

Mfg Lic No.: G/25/1486

12 Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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