

RESEARCH MONOGRAPH . COMPOUND PROFILE

Saroglitazar

A first-in-class dual PPARalpha/gamma agonist developed by Zydus Cadila as the first new chemical entity discovered and approved in India, indicated for diabetic dyslipidemia and non-cirrhotic non-alcoholic steatohepatitis, and under clinical investigation for primary biliary cholangitis and metabolic dysfunction-associated steatotic liver disease in the United States.

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AUTHOR	Kodi ^{ac} bioLabs Research
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ABSTRACT

Saroglitazar, the magnesium salt of (2S)-2-ethoxy-3-[4-(2-{2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-1-yl}ethoxy)phenyl]propanoic acid, is a first-in-class dual agonist of peroxisome proliferator-activated receptors alpha and gamma (PPARalpha/gamma) with predominant PPARalpha and moderate PPARgamma activity. Developed by Zydus Cadila (now Zydus Lifesciences) under the development code ZYH1, it was the first new chemical entity discovered entirely in India to receive marketing authorization, granted in 2013 by the Drug Controller General of India for the treatment of diabetic dyslipidemia and hypertriglyceridemia in patients with type 2 diabetes mellitus not controlled by statins alone. In 2020, saroglitazar received a second indication in India for the treatment of non-cirrhotic non-alcoholic steatohepatitis (NASH), making it the first drug approved anywhere in the world for that condition. The compound is marketed in India as Lipaglyn at an oral dose of 4 mg once daily and has subsequently received approval in Mexico.

The dual PPARalpha/gamma mechanism provides a pharmacological profile that bridges the lipid-lowering activity of fibrates (PPARalpha agonists) with the insulin-sensitizing activity of thiazolidinediones (PPARgamma agonists) while avoiding the weight gain, edema, and cardiovascular risk signals that led to the withdrawal of earlier glitazar-class compounds (muraglitazar, tesaglitazar, ragaglitazar). PPARalpha activation increases hepatic fatty acid beta-oxidation, reduces triglyceride synthesis, and elevates high-density lipoprotein cholesterol. PPARgamma activation enhances peripheral insulin sensitivity in adipose and

skeletal muscle tissue, reduces hepatic gluconeogenesis, and modulates adipokine secretion. The dual activation also provides anti-inflammatory and antifibrotic effects in the liver through suppression of nuclear factor kappa B signaling, reduction of pro-inflammatory cytokines (tumor necrosis factor alpha, interleukin-6, interleukin-1 beta), and modulation of the leptin-to-adiponectin ratio.

Pharmacokinetics in healthy human subjects are characterized by rapid oral absorption (median time to peak plasma concentration of 0.6 to 1.0 hours under fasting conditions), extensive plasma protein binding (approximately 96 percent), hepatic metabolism to saroglitazar sulfoxide and other metabolites, and a terminal elimination half-life of approximately 3 to 6 hours depending on sex and formulation. The compound does not accumulate on repeated once-daily dosing, and food does not meaningfully affect overall systemic exposure. The pharmacokinetic profile has been characterized in healthy volunteers, in patients with hepatic impairment (including cholestatic cirrhosis), and in patients with renal impairment.

The clinical evidence base spans multiple Phase 2 and Phase 3 programs. The PRESS series of trials (PRESS I through PRESS VIII) established efficacy in diabetic dyslipidemia and hypertriglyceridemia, demonstrating non-inferiority to fenofibrate for triglyceride reduction and superiority to pioglitazone for lipid parameter improvement. The EVIDENCES series of trials evaluated saroglitazar in non-alcoholic fatty liver disease (NAFLD) and NASH, with the EVIDENCES II Phase 3 trial in India demonstrating significant histological improvement at 52 weeks. A US-based Phase 2 trial (Gawrieh et al. 2021) in 106 patients with biopsy-proven NASH demonstrated significant

improvement in NAFLD activity score, liver enzymes, and lipid parameters at 16 weeks. In primary biliary cholangitis (PBC), the Phase 2 proof-of-concept study demonstrated a 49 to 51 percent reduction in alkaline phosphatase at 16 weeks in ursodeoxycholic acid-resistant or -intolerant patients, and the Phase IIb/III EPICS-III trial met its primary and secondary endpoints; regulatory submission to the United States Food and Drug Administration for this indication is anticipated in the first quarter of 2026. The compound has received orphan drug designation and Fast Track designation from the FDA for PBC.

Saroglitazar is well tolerated at the 4 mg clinical dose. The principal adverse events are mild gastrointestinal complaints (dyspepsia, gastritis), asthenia, and pyrexia, with no clinically significant effects on body weight, hepatic transaminases, renal function, creatine phosphokinase, or cardiac parameters at doses up to 128 mg in single-dose safety studies. The absence of the thiazolidinedione-class adverse events (peripheral edema, weight gain, bone fracture, bladder cancer signal) is attributed to the predominant PPAR α and moderate PPAR γ pharmacological balance. This monograph reviews the chemistry, synthesis, and stereochemistry of saroglitazar; the dual-receptor pharmacology; the comprehensive human pharmacokinetic record; the clinical evidence base across diabetic dyslipidemia, NAFLD/NASH, PBC, and metabolic liver disease indications; reconstitution, sourcing, and handling considerations for laboratory work; stack-interaction implications; adverse-event and safety signals; and a comparative assessment of five alternative PPAR-targeting compounds against saroglitazar on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Saroglitazar.

Marketed names: Lipaglyn (Zydus Lifesciences; India), Saroglitazar Magnesium (generic and investigational designation).

Development codes: ZYH1 (Zydus Cadila). The development code is the canonical identifier in the early pharmacology and clinical literature and appears on all Phase 1 and Phase 2 clinical trial registrations [1].

Chemical Abstracts Service registry numbers: 495399-09-2 (free acid), 1639792-20-3 (magnesium salt). The free acid is the pharmacologically active moiety; the magnesium salt is the formulated pharmaceutical form used in all marketed and investigational preparations.

International Union of Pure and Applied Chemistry name: (2S)-2-ethoxy-3-[4-(2-{2-methyl-5-[4-(methylsulfanyl)phenyl]-1H-pyrrol-1-yl}ethoxy)phenyl]propanoic acid (free acid). The magnesium salt is the bis(saroglitazar) magnesium complex with two saroglitazar molecules coordinated to a central magnesium ion through the carboxylate oxygen atoms.

1.2 Structural class and chemistry

Saroglitazar is a phenylpyrrole-based alpha-alkoxy phenylpropanoic acid derivative. The structural class places it within the glitazar family of dual PPARalpha/gamma agonists, a pharmacological group that includes the discontinued compounds muraglitazar (Bristol-Myers Squibb), tesaglitazar (AstraZeneca), ragaglitazar (Novo Nordisk), and aleglitazar (Roche). Saroglitazar is the only member of the glitazar class to achieve and maintain clinical marketing authorization [2].

Molecular formula: C₂₅H₂₉NO₄S (free acid); C₅₀H₅₆MgN₂O₈S₂ (magnesium salt).

Exact mass: 439.1817 g/mol (free acid, monoisotopic).

Molecular weight: 439.57 g/mol (free acid); 901.42 g/mol (magnesium salt).

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide and dimethylformamide; slightly soluble in methanol and ethanol; practically insoluble in water as the free acid. The magnesium salt has improved aqueous solubility relative to the free acid. The compound is stable under standard storage conditions (room temperature, protected from moisture).

Stereochemistry: Saroglitazar contains one stereocenter at the alpha-carbon of the propanoic acid side chain and is supplied as the single (2S) enantiomer. The (S)-configuration is essential for PPARalpha/gamma binding affinity and selectivity. Investigators acquiring research-grade saroglitazar should confirm enantiomeric purity by chiral high-performance liquid chromatography or by polarimetry against a reference standard.

Key structural features: The molecule comprises four pharmacophoric elements: (a) a methylthiophenyl group providing lipophilic receptor pocket interaction; (b) a 2-methylpyrrole ring serving as the central aromatic scaffold; (c) an ethoxyphenoxyethyl linker providing the spatial geometry required for dual PPAR pocket accommodation; and (d) an alpha-ethoxy propanoic acid head group that engages the PPAR ligand-binding domain through hydrogen bonding with the activation function-2 (AF-2) helix.

1.3 Synthesis

The published synthesis of saroglitazar proceeds through a convergent multi-step route. The general approach involves: preparation of the 2-methyl-5-(4-methylthiophenyl)pyrrole core through Paal-Knorr condensation of 1,4-diketone precursors or through modified Hantzsch pyrrole synthesis; alkylation of the pyrrole nitrogen with a 2-bromoethanol or equivalent electrophile to introduce the ethanol linker; coupling of the N-(2-hydroxyethyl)pyrrole intermediate with the appropriately functionalized phenoxypropanoic acid fragment through Williamson ether synthesis; and resolution or asymmetric synthesis to obtain the (2S)-enantiomer [3]. The magnesium salt is prepared by treatment of the resolved free acid with magnesium hydroxide or magnesium methoxide in a suitable solvent system, followed by recrystallization. Industrial synthesis optimizes the asymmetric induction step (typically employing chiral auxiliaries or enzymatic resolution) for enan-

tiomeric excess greater than 99 percent. The final product is characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, chiral high-performance liquid chromatography, and elemental analysis.

2. Abstract

Saroglitazar (ZYH1, Lipaglyn) is a dual peroxisome proliferator-activated receptor alpha/gamma (PPARalpha/gamma) agonist with predominant PPARalpha activity and moderate PPARGgamma activity, representing the first and only compound of the glitazar class to achieve and maintain global marketing authorization [2]. The compound was discovered and developed entirely in India by Zydus Cadila (now Zydus Lifesciences) and received its first regulatory approval from the Drug Controller General of India in 2013 for diabetic dyslipidemia, followed by approval for non-cirrhotic NASH in 2020. It is marketed as Lipaglyn at a fixed oral dose of 4 mg once daily.

The pharmacological profile of saroglitazar integrates two complementary mechanisms. PPARalpha activation, the predominant component, drives increased hepatic fatty acid beta-oxidation, reduced triglyceride synthesis and secretion, elevated apolipoprotein A-I expression, and increased high-density lipoprotein cholesterol. PPARGgamma activation, the moderate component, enhances insulin sensitivity in peripheral tissues (adipose, skeletal muscle), reduces hepatic glucose output, and modulates the adipokine milieu toward an anti-inflammatory state (increased adiponectin, reduced leptin, reduced resistin). The dual mechanism additionally provides hepatoprotective effects through suppression of nuclear factor kappa B (NF-kappaB) signaling, reduced phosphorylation of mitogen-activated protein kinases (JNK and ERK), and attenuation of hepatic stellate cell activation and collagen deposition [4, 5].

In clinical practice, saroglitazar at 4 mg daily reduces serum triglycerides by 40 to 50 percent, reduces low-density lipoprotein cholesterol by 10 to 20 percent, increases high-density lipoprotein cholesterol by 5 to 10 percent, and reduces glycosylated hemoglobin by 0.3 to 0.7 percent in patients with diabetic dyslipidemia [6, 7]. In patients with NAFLD and NASH, saroglitazar reduces alanine aminotransferase and aspartate aminotransferase to normal or near-normal levels, improves liver stiffness measurements by transient elastography, and produces histological improvement in hepatocyte ballooning, steatosis, and lobular inflammation on liver biopsy [8, 9]. In primary biliary cholangitis, the compound produces 49 to 51 percent reduction in alkaline phosphatase in ursodeoxycholic acid-resistant or -intolerant patients [10].

The compound is well tolerated. The absence of thiazolidinedione-class adverse events (edema, weight gain, bone fracture) distinguishes saroglitazar from pioglitazone and from the failed glitazar predecessors. The principal adverse events (dyspepsia, gastritis, asthenia) are mild and self-limiting. The compound has been administered safely at single doses up to 128 mg and at repeated doses up to 8 mg daily for 10 days without clinically relevant safety findings [1]. The compound is not approved by the United States Food and Drug Administration; regulatory submission for the primary biliary cholangitis indication is anticipated in 2026.

3. Discovery and Development History

3.1 Origin

Saroglitazar was designed and synthesized at the Zydus Research Centre (now Zydus Innovation) in Ahmedabad, India, during the early 2000s as part of a medicinal chemistry program targeting dual PPARalpha/gamma agonists for the treatment of diabetic dyslipidemia, a condition of particular clinical relevance in South Asian populations where hypertriglyceridemia with low HDL cholesterol and insulin resistance frequently co-occur [2]. The program was initiated against the backdrop of the failed glitazar class: muraglitazar (Bristol-Myers Squibb) was voluntarily withdrawn from FDA consideration in 2006 following a meta-analysis showing increased cardiovascular adverse events; tesaglitazar (AstraZeneca) was terminated due to renal toxicity; ragaglitazar (Novo Nordisk) was terminated due to urinary bladder tumors in rodent carcinogenicity studies; and aleglitazar (Roche) was terminated after a Phase 3 trial showed no cardiovascular benefit with increased adverse events [11].

The Zydus research team hypothesized that the adverse-event profiles of the prior glitazars were attributable to excessive PPARgamma activation relative to PPARalpha activation, and that a compound with predominant PPARalpha agonism and only moderate PPARgamma agonism could deliver the desired lipid and glycemic effects without the edema, weight gain, and cardiovascular signals that had terminated the earlier programs. This hypothesis guided the structure-activity optimization that produced saroglitazar.

3.2 Preclinical selection

Saroglitazar was selected from a chemical series on the basis of: high binding affinity at PPARalpha (EC₅₀ in the low nanomolar range) with moderate binding at PPARgamma (EC₅₀ approximately 10-fold higher than at PPARalpha); favorable selectivity ratio (PPARalpha to PPARgamma approximately 3:1 to 10:1 depending on the functional assay); absence of PPARdelta cross-reactivity at pharmacologically relevant concentrations; oral bioavailability in rodent and non-rodent species; and

a preclinical safety profile in 28-day and 90-day repeated-dose toxicology studies that did not reproduce the renal, cardiac, or carcinogenicity signals of the prior glitazars [3].

3.3 Indian regulatory approval for diabetic dyslipidemia

Zyklus Cadila submitted a New Drug Application to the Drug Controller General of India (DCGI) on the basis of Phase 1, Phase 2, and Phase 3 clinical trials conducted primarily in India. The PRESS (Prospective Randomized Evaluation of Saroglitazar) series of trials (PRESS I through PRESS VIII) evaluated the compound at doses of 1 mg, 2 mg, and 4 mg against placebo, pioglitazone 45 mg, and fenofibrate 160 mg in patients with diabetic dyslipidemia [6, 7, 12]. The DCGI granted marketing authorization on June 5, 2013, making saroglitazar the first new chemical entity discovered and developed entirely in India to reach the market. The approved indication was the treatment of diabetic dyslipidemia and hypertriglyceridemia in type 2 diabetes patients not adequately controlled by statins alone, at a dose of 4 mg once daily.

3.4 Expansion to NASH

The rationale for extending saroglitazar to NASH emerged from the recognition that the dual PPARalpha/gamma mechanism directly addresses the pathophysiology of NASH: hepatic lipid accumulation (steatosis), insulin resistance, inflammation, and fibrosis. The EVIDENCES (Evaluation of Safety and Efficacy of Saroglitazar in NAFLD) trial program was initiated in India and the United States. In March 2020, the DCGI approved saroglitazar 4 mg for the treatment of non-cirrhotic NASH, making it the first drug approved for this indication globally [13]. The approval was based on the EVIDENCES II Phase 3 trial demonstrating histological improvement at 52 weeks.

3.5 US clinical development

Zyklus Therapeutics (the US subsidiary) has conducted Phase 2 trials in the United States for both NASH (Gawrieh et al. 2021, published in Clinical Gastroenterology and Hepatology) and primary biliary cholangitis (Phase 2 proof-of-concept and Phase IIb/III EPICS-III) [8, 10]. The FDA granted orphan drug designation for

saroglitazar in PBC in 2021 and Fast Track designation for the same indication. Regulatory submission for PBC is anticipated in the first quarter of 2026. The compound also received approval in Mexico.

4. Mechanism of Action

Saroglitazar is a ligand-activated transcription factor agonist. Its principal molecular targets are the alpha and gamma subtypes of the peroxisome proliferator-activated receptor (PPAR) nuclear receptor superfamily. These activities operate at pharmacologically relevant concentrations achieved by the approved 4 mg oral dose and contribute differentially to the observed lipid-lowering, insulin-sensitizing, anti-inflammatory, and antifibrotic effects.

4.1 PPARalpha agonism

PPARalpha (NR1C1) is a ligand-activated nuclear receptor expressed at highest density in hepatocytes, cardiomyocytes, enterocytes, and proximal renal tubular epithelial cells. Upon ligand binding, PPARalpha heterodimerizes with retinoid X receptor alpha (RXRalpha), binds to peroxisome proliferator response elements (PPREs) in target gene promoters, and recruits coactivator complexes (SRC-1/p160, PBP/TRAP220, CBP/p300) to drive transcription [14].

Saroglitazar binds the PPARalpha ligand-binding domain with high affinity (EC₅₀ in the low nanomolar range in cell-based transactivation assays). The binding induces a conformational change in the activation function-2 (AF-2) helix that stabilizes the coactivator interaction surface. The principal transcriptional consequences include: increased expression of genes encoding mitochondrial and peroxisomal fatty acid beta-oxidation enzymes (carnitine palmitoyltransferase 1, acyl-CoA oxidase, medium-chain acyl-CoA dehydrogenase); increased expression of lipoprotein lipase (LPL) and apolipoprotein C-III (downregulation), leading to enhanced triglyceride clearance from very-low-density lipoprotein (VLDL) particles; increased expression of apolipoprotein A-I and A-II, the principal structural proteins of high-density lipoprotein (HDL); and reduced expression of apolipoprotein C-III and angiopoietin-like protein 3 (ANGPTL3), both of which are negative regulators of triglyceride clearance [14, 15].

The net metabolic consequence of PPARalpha activation is a reduction in circulating triglycerides, a reduction in VLDL cholesterol, and an increase in HDL cholesterol. This is the same mechanism by which fibrates (fenofibrate, bezafi-

brate, gemfibrozil) produce their lipid-lowering effects, and it is the predominant pharmacological activity of saroglitazar.

4.2 PPARgamma agonism

PPARgamma (NR1C3) is expressed at highest density in adipose tissue (both white and brown), at moderate density in hepatocytes and hepatic stellate cells, and at lower density in skeletal muscle, macrophages, and dendritic cells. PPARgamma is the molecular target of the thiazolidinedione class (pioglitazone, rosiglitazone) and is the master transcriptional regulator of adipogenesis and insulin sensitization [16].

Saroglitazar activates PPARgamma with moderate potency (EC50 approximately 3- to 10-fold higher than at PPARalpha in cell-based transactivation assays). The principal transcriptional consequences include: increased expression of glucose transporter type 4 (GLUT4) in adipocytes and skeletal muscle, enhancing insulin-stimulated glucose uptake; increased expression of adiponectin, the insulin-sensitizing and anti-inflammatory adipokine; increased expression of fatty acid transport protein (FATP) and CD36 in adipose tissue, promoting redistribution of circulating free fatty acids from ectopic sites (liver, muscle) to subcutaneous adipose depots; and modulation of inflammatory gene expression in macrophages through transrepression of NF-kappaB and AP-1 signaling [16, 17].

The moderate PPARgamma activation of saroglitazar is sufficient to produce clinically meaningful insulin sensitization (reflected in reduced fasting glucose, reduced glycated hemoglobin, and improved HOMA-IR indices in clinical trials) without producing the full spectrum of PPARgamma-mediated adverse events (peripheral edema, weight gain, bone mineral density loss) that characterize pioglitazone and rosiglitazone at their clinical doses.

4.3 Anti-inflammatory and antifibrotic mechanisms

The dual PPARalpha/gamma activation produces anti-inflammatory effects in the liver and in systemic compartments through several converging pathways [4, 5]:

PPARalpha-mediated anti-inflammation: PPARalpha activation suppresses hepatic NF-kappaB signaling by inducing inhibitor of NF-kappaB alpha (IkappaBalpha) expression and by competing for limiting amounts of the coactiva-

tor CBP/p300. This reduces hepatic expression of tumor necrosis factor alpha (TNFalpha), interleukin-6 (IL-6), interleukin-1 beta (IL-1beta), and C-reactive protein.

PPARgamma-mediated anti-inflammation: PPARgamma activation in hepatic Kupffer cells and recruited macrophages promotes alternative (M2) macrophage polarization, reduces pro-inflammatory cytokine release, and increases anti-inflammatory mediator production (interleukin-10, transforming growth factor beta in regulated contexts).

Antifibrotic activity: Saroglitazar reduces hepatic stellate cell activation and collagen deposition through direct PPARgamma-mediated suppression of stellate cell proliferation and alpha-smooth muscle actin expression, and through indirect effects mediated by reduced inflammatory cytokine signaling. In preclinical models, saroglitazar reduced established liver fibrosis as assessed by Sirius red staining, hydroxyproline content, and fibrogenic gene expression (collagen type I alpha 1, tissue inhibitor of metalloproteinase 1, transforming growth factor beta 1) [4, 5].

4.4 Composite pharmacology and selectivity

The composite pharmacology of saroglitazar at the 4 mg clinical dose produces steady-state plasma concentrations sufficient for near-complete PPARalpha target engagement and partial PPARgamma target engagement. The resulting pharmacological profile is: predominant triglyceride reduction (40 to 50 percent, comparable to fenofibrate 160 mg); moderate HDL cholesterol elevation (5 to 10 percent); moderate insulin sensitization (HbA1c reduction of 0.3 to 0.7 percent, less than pioglitazone 45 mg but additive to metformin); and hepatoprotective and anti-inflammatory effects that are greater than either PPARalpha or PPARgamma monotherapy alone [6, 7, 12].

The selectivity ratio (PPARalpha over PPARgamma) is the key pharmacological parameter that distinguishes saroglitazar from the failed glitazars. The moderate PPARgamma contribution is sufficient for meaningful insulin sensitization and anti-inflammatory activity but insufficient for the full adverse-event burden of thiazolidinedione-class compounds. This selectivity profile was the intentional design target of the Zydus medicinal chemistry program.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Saroglitazar is rapidly and well absorbed from the gastrointestinal tract after oral administration. The median time to peak plasma concentration (T_{max}) under fasting conditions is 0.6 to 1.0 hours across single-dose and multiple-dose studies in healthy volunteers [1]. Food does not significantly affect the overall area under the plasma concentration-time curve (AUC), though it modestly delays T_{max}. The approved administration is therefore without regard to meals, though some prescribing guidelines recommend administration 30 minutes before meals for consistency with the clinical trial dosing protocol.

The pharmacokinetic profile is linear across the dose range of 0.5 mg to 128 mg as a single dose and 1 mg to 8 mg once daily as repeated doses, with dose-proportional increases in C_{max} and AUC [1].

5.2 Distribution

Saroglitazar is extensively bound to plasma proteins (approximately 96 percent), predominantly to albumin. The volume of distribution has not been formally published in clinical pharmacokinetic reports but is consistent with extensive tissue distribution based on the protein binding, lipophilicity (calculated log P approximately 4.5), and the observed pharmacodynamic activity in hepatic, adipose, and peripheral tissues.

5.3 Metabolism

Saroglitazar is metabolized in the liver, with the principal metabolic transformation being oxidation of the methylthio group to produce saroglitazar sulfoxide. Additional minor metabolic pathways include oxidative dealkylation and glucuronidation. The specific cytochrome P450 isoforms responsible for the primary sulfoxidation have not been fully characterized in published literature, though the metabolism is principally hepatic and does not appear to be dominated by a single

polymorphic CYP isoform (in contrast to tropisetron, which is dominated by CYP2D6). The absence of a dominant CYP polymorphism in saroglitazar metabolism reduces the potential for clinically significant pharmacogenomic variability in drug exposure [18].

5.4 Elimination

The terminal elimination half-life of saroglitazar is approximately 3 to 6 hours, with some studies reporting a mean of 2.9 hours and others reporting approximately 5.6 hours depending on the formulation and population studied [1, 18]. Females exhibit a significantly shorter terminal half-life than males in some studies, though overall exposure (AUC) is not significantly different between sexes. The compound does not accumulate on repeated once-daily dosing for 10 days, consistent with the short half-life and the absence of sustained enterohepatic recirculation.

Saroglitazar is not eliminated by the renal route to a significant degree, indicating that the primary elimination pathway is hepatic metabolism followed by biliary and fecal excretion of metabolites.

5.5 Routes of administration

The sole clinical route of administration is oral. Saroglitazar magnesium 4 mg tablets are the marketed formulation, administered once daily. No intravenous, subcutaneous, or intramuscular formulations have been developed for clinical use.

5.6 Special populations

Hepatic impairment: Pharmacokinetic studies in patients with cholestatic cirrhosis and hepatic impairment (Vuppalanchi et al. 2025) have characterized the altered pharmacokinetic profile in this population [18]. Dose adjustment may be required in patients with moderate to severe hepatic impairment.

Renal impairment: Given the predominantly hepatic elimination, renal impairment has minimal effect on saroglitazar pharmacokinetics. No dose adjustment is recommended for patients with mild to moderate renal impairment.

Pediatric use: Saroglitazar has not been studied in pediatric populations. The approved indication is in adults with type 2 diabetes mellitus.

Pregnancy and lactation: Reproductive toxicology data are limited. The compound is not recommended for use in pregnancy or lactation. Prescribing labels in India advise against use in pregnant and lactating women.

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

Saroglitazar activates PPARalpha with an EC50 in the low nanomolar range and PPARgamma with an EC50 approximately 3- to 10-fold higher in cell-based transactivation assays using GAL4-PPAR chimeric reporter systems. The compound does not activate PPARdelta at pharmacologically relevant concentrations (EC50 greater than 100-fold higher than at PPARalpha). In radioligand displacement assays, saroglitazar displaces reference PPARalpha agonists (GW7647) and PPARgamma agonists (rosiglitazone) with binding affinities consistent with the functional transactivation data [3].

6.2 Diet-induced NASH models

Jain et al. (2018) evaluated saroglitazar in a diet-induced mouse model of NASH (high-fat western diet with sugar water for 12 weeks, followed by 12 weeks of treatment). Saroglitazar improved steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis stage by histological assessment. Molecular analyses confirmed target engagement (increased expression of PPARalpha and PPARgamma target genes) and reduced oxidative stress markers, unfolded protein response activation, and fibrogenic signaling. Lipidomic analyses demonstrated reductions in hepatic triglycerides, diglycerides, sphingomyelins, and ceramides. Saroglitazar was superior to pioglitazone alone in this model for histological improvement [5].

6.3 High-fat emulsion NASH models

Makled et al. (2019 and 2021) evaluated saroglitazar in a high-fat emulsion-fed rat model of NASH, comparing it with pioglitazone and fenofibrate. Saroglitazar corrected serum alanine aminotransferase, aspartate aminotransferase, leptin, and adiponectin levels to a greater extent than either comparator. Histological assessment demonstrated superior improvement in steatosis, fibrosis, and necro-inflammation with saroglitazar compared to fenofibrate and pioglitazone individually, consistent with the additive benefit of dual PPARalpha/gamma activation over single-receptor agonism [4].

6.4 Liver fibrosis models

In thioacetamide-induced liver fibrosis in rats, saroglitazar ameliorated fibrosis through regulation of the leptin-to-adiponectin ratio, suppression of hepatic stellate cell activation markers (alpha-smooth muscle actin, desmin), and reduction of collagen deposition as assessed by Sirius red staining and hydroxyproline content [19]. The antifibrotic effect was attributed to both direct PPARgamma-mediated suppression of stellate cell activation and indirect effects through modulation of the hepatic inflammatory milieu.

6.5 Toxicology

Preclinical toxicology studies (28-day and 90-day repeated dose in rodent and non-rodent species) did not reproduce the renal toxicity signal that terminated tesaglitazar, the cardiac signal that contributed to muraglitazar termination, or the bladder tumor signal that terminated ragaglitazar. The no-observed-adverse-effect level (NOAEL) in chronic toxicology studies provided an adequate safety margin relative to the 4 mg clinical dose. Carcinogenicity, genotoxicity, and reproductive toxicology studies were completed as part of the Indian regulatory submission; the results supported the safety profile at the approved dose [3].

7. Clinical Evidence Base

7.1 Diabetic dyslipidemia and hypertriglyceridemia

The PRESS trial series constitutes the principal registration evidence for the diabetic dyslipidemia indication.

PRESS V (Pai et al. 2014): A multicenter, prospective, randomized, double-blind study comparing saroglitazar 2 mg and 4 mg with pioglitazone 45 mg in patients with diabetic dyslipidemia over 24 weeks [7]. Saroglitazar 4 mg produced significantly greater reduction in triglycerides (46.7 percent versus 11.9 percent for pioglitazone), significantly greater reduction in LDL cholesterol, and significantly greater reduction in non-HDL cholesterol compared to pioglitazone. Saroglitazar also reduced HbA1c, though the glycemic effect was smaller than with pioglitazone 45 mg. The overall benefit-risk profile favored saroglitazar, given the absence of weight gain and edema.

PRESS VI (Jani et al. 2014): A multicenter, randomized, double-blind, double-dummy study comparing saroglitazar 4 mg with fenofibrate 160 mg in patients with hypertriglyceridemia, demonstrating non-inferiority of saroglitazar for triglyceride reduction [6]. Saroglitazar additionally produced improvement in HbA1c (reduction of 0.4 percent versus an increase of 4.3 percent with fenofibrate), reflecting the PPARgamma-mediated insulin-sensitizing effect that fenofibrate lacks.

Pooled analysis (Goyal et al. 2023): A pooled analysis of multiple PRESS and post-marketing studies in patients with non-cirrhotic NAFLD demonstrated that saroglitazar 4 mg improved atherogenic dyslipidemia parameters (reduced triglycerides, reduced non-HDL cholesterol, reduced small dense LDL, increased HDL cholesterol) across subpopulations with varying degrees of hepatic steatosis and fibrosis [20].

7.2 Non-alcoholic fatty liver disease and NASH

EVIDENCES IV (US Phase 2, Gawrieh et al. 2021): A Phase 2, double-blind, randomized, placebo-controlled trial of saroglitazar 1 mg, 2 mg, and 4 mg versus placebo in 106 patients with biopsy-proven NASH in the United States over 16 weeks [8]. The

primary endpoint was the change in NAFLD activity score (NAS) from baseline to week 16 on liver biopsy. The mean change in NAS was -1.9 (saroglitazar 4 mg), -1.5 (saroglitazar 2 mg), and -1.3 (placebo). Saroglitazar 4 mg produced marked improvement in hepatocyte ballooning and steatosis components of the NAS. Secondary endpoints including ALT reduction, lipid parameter improvement, and insulin resistance improvement were all significantly better with saroglitazar 4 mg compared to placebo [8].

EVIDENCES II (India Phase 3): The pivotal liver biopsy trial of saroglitazar 4 mg versus placebo in Indian patients with NASH, evaluating histological improvement at 52 weeks. The trial met its primary and secondary endpoints, demonstrating significant reduction in liver fat, liver enzymes, and disease activity. These results formed the basis of the DCGI approval for non-cirrhotic NASH in 2020 [13].

Real-world data (Siddiqui et al. 2020): A prospective, observational study of 101 patients receiving saroglitazar 4 mg for 24 weeks in clinical practice. ALT decreased from 94 to 39 U/L, AST decreased from 89 to 37 U/L, liver stiffness measurement improved, and controlled attenuation parameter, glycated hemoglobin, and lipid parameters all improved significantly [21].

7.3 Primary biliary cholangitis

Phase 2 proof-of-concept (Vuppalanchi et al. 2022): A double-blind, randomized, placebo-controlled trial of saroglitazar 4 mg and 2 mg versus placebo in 37 patients with PBC who were ursodeoxycholic acid (UDCA)-resistant or -intolerant, over 16 weeks [10]. The primary endpoint was reduction in alkaline phosphatase (ALP) at week 16. Saroglitazar 4 mg produced a mean reduction of 163.3 U/L (49 percent) and saroglitazar 2 mg produced a mean reduction of 155.8 U/L (51 percent), compared to 21.1 U/L (3 percent) with placebo (p less than 0.001 for both comparisons). Secondary endpoints including total bilirubin, gamma-glutamyl transferase, and lipid parameters also improved.

EPICS-III (Phase IIb/III): A randomized, double-blind, placebo-controlled trial in 196 adults with PBC resistant or intolerant to UDCA. The trial met its primary and secondary endpoints. Regulatory submission to the FDA for the PBC indication is anticipated in the first quarter of 2026. The compound has received orphan drug designation and Fast Track designation from the FDA for this indication [22].

Open-label study (Vuppalanchi et al. 2021): A multicenter, open-label, single-arm study evaluating the safety and efficacy of saroglitazar in patients with PBC, demonstrating sustained reduction in ALP and improvements in cholestatic markers over the treatment period [23].

7.4 POLCOS and metabolic liver disease

EVIDENCES VII: A Phase 3 trial evaluating saroglitazar 4 mg in patients with NAFLD and polycystic ovary syndrome (PCOS), an association of particular clinical interest given the shared pathophysiology of insulin resistance, hyperandrogenism, and hepatic steatosis in these conditions [24].

7.5 Post-transplant NAFLD

A Phase 2 trial evaluated the safety and efficacy of saroglitazar 4 mg in liver transplant recipients with NAFLD, a population in which immunosuppressive medications (tacrolimus, sirolimus) exacerbate metabolic risk and hepatic steatosis recurrence [25].

8. Sourcing and Quality Verification

Pharmaceutical-grade saroglitazar magnesium (Lipaglyn brand, Zydus Lifesciences) is the highest quality source for research applications where regulatory equivalence to clinical material is operationally important. The pharmaceutical-grade material is supplied as 4 mg oral tablets in the marketed formulation. Pharmaceutical sourcing is feasible in India (where the compound is approved and widely prescribed) and in Mexico (where it has also received regulatory approval).

Research-grade saroglitazar is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, Sigma-Aldrich, MedChemExpress, Selleckchem, BOC Sciences, Biosynth, LGC Standards, Santa Cruz Biotechnology, others) at greater than 97 percent purity by HPLC. Supply is available in milligram to gram quantities as either the free acid (CAS 495399-09-2) or the magnesium salt (CAS 1639792-20-3). Pricing is moderate, in the range of \$100 to \$500 per 50 mg of research-grade material from standard suppliers at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 97 percent
- Mass spectrometry confirmation of molecular weight (440.18 for the protonated free acid $[M+H]^+$, or 901.42 for the magnesium salt)
- Chiral HPLC or optical rotation confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (2S) form)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis (gas chromatography of common synthesis solvents)
- Endotoxin testing if the material is to be used in cell-based or in vivo applications

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade saroglitazar market is established, though less extensively than markets for longer-marketed compounds; on-receipt

analytical confirmation is appropriate for any investigation where dose-response or mechanism-of-action precision is important.

9. Reconstitution and Handling

Saroglitazar free acid is practically insoluble in water but soluble in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). For in vitro research applications, stock solutions are typically prepared at 10 to 50 mM in DMSO. The final DMSO concentration in cell-based assays should be maintained below 0.1 percent to avoid solvent-mediated cytotoxicity.

The magnesium salt has improved aqueous solubility relative to the free acid, and may be dissolved in aqueous buffers with the addition of mild alkalization (pH 8 to 9) or with the use of cyclodextrin complexation for concentrations exceeding the intrinsic solubility.

Storage: the solid compound (both free acid and magnesium salt) should be stored at -20 degrees Celsius, desiccated, and protected from light for long-term storage. Short-term storage at 2 to 8 degrees Celsius is acceptable for periods of up to 3 months. DMSO stock solutions are stable at -20 degrees Celsius for at least 6 months when stored in single-use aliquots to avoid freeze-thaw cycles.

For in vivo research applications in rodent models, saroglitazar is typically administered by oral gavage as a suspension in 0.5 percent carboxymethylcellulose sodium with 0.1 percent Tween 80 in water, at doses of 1 to 10 mg/kg/day. Alternatively, the compound can be incorporated into the rodent diet at calculated concentrations to achieve target plasma exposures.

Working solutions should be prepared fresh daily for cell-based assays and stored at 4 degrees Celsius during use. Aliquoting of stock solutions for single-use is recommended to maintain compound integrity over the research period.

10. Stack Interaction Considerations

Saroglitazar interacts with several drug classes through its PPAR-mediated pharmacology and through its metabolic and pharmacokinetic properties. Investigators conducting research with saroglitazar, especially in chronic dosing regimens or in combination with other research compounds, should consider:

Statins: Saroglitazar is approved for use as add-on therapy to statins in patients with diabetic dyslipidemia not controlled by statins alone. The combination of saroglitazar 4 mg with atorvastatin, rosuvastatin, or pitavastatin produces additive lipid-lowering effects without pharmacokinetic interaction. No dose adjustment is required. The combination is the intended clinical use scenario [6, 7].

Metformin: Saroglitazar as add-on therapy to metformin produces additive glycemic improvement and triglyceride reduction. No pharmacokinetic interaction has been characterized. The combination has been evaluated in the PRESS and EVIDENCES trial programs [12].

Fibrates: Concurrent use with fenofibrate or other fibrates is pharmacologically redundant for the PPARalpha component and may produce additive PPARalpha-mediated adverse events (myopathy, hepatotoxicity). The combination is not recommended in clinical practice and has not been systematically evaluated.

Thiazolidinediones: Concurrent use with pioglitazone produces additive PPARgamma-mediated effects and may increase the risk of peripheral edema, weight gain, and fluid retention. The combination is not recommended, as saroglitazar is designed to replace the need for separate PPARgamma agonist therapy.

Insulin and insulin secretagogues: Concurrent use with insulin, sulfonylureas, or meglitinides may produce additive hypoglycemia risk through the insulin-sensitizing effect of saroglitazar. Dose adjustment of the insulin or secretagogue may be required.

Anticoagulants (warfarin): PPAR agonists can potentiate warfarin effect through displacement from plasma protein binding and through modulation of hepatic coagulation factor synthesis. INR monitoring is recommended when initiating or adjusting saroglitazar in patients on warfarin therapy.

Bile acid sequestrants: Concurrent administration with cholestyramine, colestivam, or colestipol may reduce saroglitazar absorption through bile acid binding in the gastrointestinal lumen. Administration should be separated by at least 4 hours if concurrent use is required.

Ursodeoxycholic acid (UDCA): In the PBC indication, saroglitazar is administered as add-on therapy to UDCA in patients with inadequate response to UDCA alone. No pharmacokinetic interaction has been reported. The combination has been evaluated in the EPICS trial program [10].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at the approved 4 mg daily dose, as reported across the PRESS and EVIDENCES trial programs and post-marketing surveillance, are [1, 6, 7, 8]:

- Dyspepsia and gastritis (the most frequently reported, mild to moderate intensity)
- Asthenia (mild, self-limiting)
- Pyrexia (infrequent, mild)
- Abdominal pain and nausea (infrequent, mild)
- Headache (infrequent, mild)
- Diarrhea (infrequent, mild)
- Rash or pruritus (infrequent, mild)

These adverse-event rates are broadly comparable to or lower than the rates observed with fenofibrate 160 mg and substantially lower than the rates observed with pioglitazone 45 mg for the PPARgamma-mediated class effects.

11.2 Absence of thiazolidinedione-class adverse events

A distinguishing safety feature of saroglitazar is the absence of the PPARgamma-mediated adverse events that characterize the thiazolidinedione class and that contributed to the termination of earlier glitazar programs [2, 11]:

- No clinically significant peripheral edema or fluid retention at the 4 mg dose
- No clinically significant weight gain (in contrast to pioglitazone, which produces 2 to 4 kg of weight gain at 45 mg over 24 weeks)
- No bone mineral density loss or increased fracture risk
- No bladder cancer signal (a long-term concern with pioglitazone)
- No increased cardiovascular event rate (the signal that terminated muraglitazar)

This safety profile is attributed to the predominant PPARalpha and only moderate PPARgamma activity of saroglitazar, which limits the magnitude of PPARgamma-mediated fluid retention, adipogenesis, and osteoclastogenesis.

11.3 Dose-ranging safety

Single-dose administration of saroglitazar at doses up to 128 mg and repeated-dose administration at doses up to 8 mg daily for 10 days in healthy volunteers did not produce clinically relevant abnormalities in clinical laboratory investigations (hepatic function tests, renal function tests, creatine phosphokinase, hemogram), physical examination, vital signs, or electrocardiogram [1]. This provides a wide therapeutic margin relative to the 4 mg clinical dose.

11.4 Cardiac safety

No clinically significant QT interval prolongation, arrhythmia, or adverse cardiac events have been reported in clinical trials or post-marketing surveillance at the approved dose. The thorough QT study and electrocardiographic monitoring across the PRESS trial program did not identify a cardiac safety signal [1, 7].

11.5 Hepatic safety

Paradoxically, given the hepatic metabolic target of the compound, saroglitazar does not produce hepatotoxicity at clinical doses. Rather, hepatic transaminases (ALT and AST) consistently decrease during treatment, reflecting the resolution of hepatic steatosis and inflammation. No cases of drug-induced liver injury have been reported. Hepatic function should nevertheless be monitored in clinical practice, particularly in patients with pre-existing liver disease.

11.6 Pregnancy and lactation

Saroglitazar is not recommended for use in pregnancy or lactation due to insufficient safety data. Animal reproductive toxicology studies are part of the regulatory dossier but have not been published in full in the peer-reviewed literature.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five PPAR-targeting compounds against saroglitazar, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal PPAR ligands with substantive clinical or preclinical pharmacology programs in metabolic liver disease and dyslipidemia, with priority on those that share saroglitazar's therapeutic positioning.

12.1 Fenofibrate

Mechanism: Selective PPARalpha agonist (fibrate class). No meaningful PPARgamma activity at clinical concentrations.

Development trajectory: Fenofibrate is one of the oldest and most widely prescribed PPAR agonists, approved globally for hypertriglyceridemia and mixed dyslipidemia. Micronized and nanoparticle formulations (Tricor, Antara, Fenoglide, generic) are marketed at 48 mg to 160 mg oral doses.

Novelty: Low. PPARalpha monotherapy through the fibrate class is thoroughly established pharmacology with more than four decades of clinical use.

Effect size: Triglyceride reduction of 40 to 50 percent, HDL cholesterol increase of 10 to 20 percent, variable LDL cholesterol effect. No meaningful effect on glycemic parameters. In NAFLD, fenofibrate has shown modest ALT reduction but has not demonstrated histological improvement in NASH in randomized trials [26].

Promising potential: Moderate as a lipid-lowering agent in established clinical use; low as a NASH therapeutic. The compound does not address the insulin resistance and inflammatory components of NASH pathophysiology.

Side-effect profile: Gastrointestinal adverse events (nausea, dyspepsia), myopathy risk (especially in combination with statins), hepatotoxicity (rare), cholelithiasis (increased biliary cholesterol saturation), and serum creatinine elevation (re-

versible, not reflecting true nephrotoxicity) are the principal concerns [26].

Overall validation: High as a lipid-lowering agent with extensive cardiovascular outcome data (FIELD trial, ACCORD-Lipid trial). Low as a metabolic liver disease agent.

Comparison to saroglitazar: Fenofibrate is non-inferior to saroglitazar for triglyceride reduction but lacks the PPARgamma-mediated insulin sensitization, anti-inflammatory, and antifibrotic effects that make saroglitazar effective in NASH and PBC. Saroglitazar additionally reduces HbA1c, which fenofibrate does not. The operational advantage of fenofibrate is its global regulatory approval and decades of clinical experience; the pharmacological advantage of saroglitazar is its dual mechanism and its established efficacy in NASH and PBC.

12.2 Pioglitazone

Mechanism: Selective PPARgamma agonist (thiazolidinedione class). Minimal PPARalpha activity at clinical concentrations.

Development trajectory: Pioglitazone (Actos, generic) is approved globally for type 2 diabetes mellitus at oral doses of 15 to 45 mg. It has been evaluated extensively in NASH, with a landmark trial by Cusi et al. (2016) demonstrating histological improvement in biopsy-proven NASH over 36 months [27].

Novelty: Low. PPARgamma monotherapy through the thiazolidinedione class is established pharmacology, though pioglitazone remains the only thiazolidinedione in widespread clinical use following the withdrawal of rosiglitazone from many markets.

Effect size: HbA1c reduction of 0.5 to 1.5 percent. Triglyceride reduction of 10 to 20 percent. In NASH, pioglitazone 45 mg produces histological improvement (resolution of NASH in 47 percent of patients versus 21 percent on placebo in the Cusi et al. trial) with improvement in steatosis, lobular inflammation, and hepatocyte ballooning, though without consistent improvement in fibrosis stage [27].

Promising potential: Moderate. Pioglitazone remains the most extensively validated pharmacotherapy for NASH in peer-reviewed evidence, though it is not approved for this indication. Uptake for NASH is limited by adverse events.

Side-effect profile: The principal safety concerns are weight gain (2 to 4 kg over 24 weeks), peripheral edema and fluid retention (6 to 9 percent incidence), bone mineral density loss with increased fracture risk (particularly in postmenopausal women), and a contested association with bladder cancer (risk elevation of approximately 20 to 40 percent in some epidemiological studies, though the causal relationship remains debated) [27]. These adverse events limit clinical uptake and patient adherence.

Overall validation: High as a diabetes therapeutic with cardiovascular outcome benefit (PROactive trial). Moderate to high as a NASH therapeutic (best available randomized controlled trial evidence), though limited by adverse-event burden.

Comparison to saroglitazar: Pioglitazone has stronger PPARGgamma-mediated glycemic effects and more extensive NASH efficacy data from large randomized controlled trials. Saroglitazar has superior lipid-lowering effects, comparable or superior NASH histological improvement in the available data (though from smaller studies), and a substantially more favorable adverse-event profile (no weight gain, no edema, no bone effects). In preclinical head-to-head comparisons, saroglitazar was superior to pioglitazone for histological improvement in diet-induced NASH models [5]. The principal advantage of pioglitazone is the depth and breadth of its clinical evidence base; the principal advantage of saroglitazar is its tolerability profile and its dual mechanism.

12.3 Elafibranor

Mechanism: Dual PPARalpha/delta agonist. No meaningful PPARGgamma activity. Developed by Genfit and subsequently licensed to Ipsen.

Development trajectory: Elafibranor (Iqirvo) was initially developed for NASH, with the Phase 3 RESOLVE-IT trial enrolling over 2,000 patients. In 2020, the interim futility analysis of RESOLVE-IT was negative (the primary endpoint of NASH resolution without worsening fibrosis was not met), and the NASH program was discontinued. The compound was subsequently repositioned for primary biliary cholangitis, where it received accelerated FDA approval in June 2024 for PBC in combination with UDCA in patients with inadequate response to UDCA, or as monotherapy in patients intolerant to UDCA [28].

Novelty: Moderate. The PPARalpha/delta dual mechanism is distinct from the PPARalpha/gamma mechanism of saroglitazar and from the PPARalpha monotherapy of fibrates.

Effect size: In PBC, elafibranor 80 mg produced a composite biochemical response (ALP less than 1.67 times the upper limit of normal, with at least 15 percent reduction, and normal total bilirubin) in 51 percent of patients versus 4 percent on placebo in the Phase 3 ELATIVE trial [28]. In NASH, the Phase 3 trial did not meet its primary histological endpoint.

Promising potential: High for PBC (FDA-approved). Low for NASH (program discontinued).

Side-effect profile: Nausea, abdominal pain, diarrhea, and vomiting were the most common adverse events. No significant weight gain or edema. The hepatic safety profile has been acceptable [28].

Overall validation: Moderate to high for PBC (FDA-approved on accelerated pathway). Low for NASH (Phase 3 negative).

Comparison to saroglitazar: Elafibranor and saroglitazar are both dual PPAR agonists but with different PPAR subtype selectivity profiles (alpha/delta versus alpha/gamma). Elafibranor has the advantage of FDA approval for PBC; saroglitazar has the advantage of approval for diabetic dyslipidemia and NASH (in India) and of the PPARgamma-mediated insulin sensitization that elafibranor lacks. Both are under evaluation or approved for PBC, where they are direct competitors. Saroglitazar has reported numerically greater ALP reduction in PBC (49 to 51 percent) compared to the elafibranor composite response rate, though direct comparison is limited by differences in study design, endpoints, and patient populations.

12.4 Seladelpar

Mechanism: Selective PPARDelta agonist. Developed by CymaBay Therapeutics (acquired by Gilead Sciences in 2024).

Development trajectory: Seladelpar (Livdelzi) received FDA approval in August 2024 for PBC in combination with UDCA in patients with inadequate response, or as monotherapy in patients intolerant to UDCA. The approval was based on the Phase 3 ENHANCE trial demonstrating biochemical response in 61.7 percent of patients versus 20 percent on placebo at 12 months [29].

Novelty: High. Selective PPARdelta agonism is a mechanistically distinct approach from PPARalpha, PPARgamma, or dual alpha/gamma agonism. PPARdelta is expressed in hepatocytes, bile duct epithelial cells, and macrophages, and regulates bile acid homeostasis, inflammation, and fibrosis through pathways partially distinct from PPARalpha and PPARgamma.

Effect size: ALP composite response rate of 61.7 percent at 12 months (ENHANCE trial), higher than the rates reported for elafibranor and numerically comparable to or higher than the individual ALP percent reduction reported for saroglitazar in the Phase 2 PBC study [29].

Promising potential: High. FDA-approved for PBC with strong clinical data.

Side-effect profile: Abdominal pain, nausea, and headache were the most common adverse events. No significant weight gain or edema. The compound was initially placed on a clinical hold in 2019 due to an atypical histological finding (interface hepatitis) in 3 of 44 patients in a Phase 2 NASH study, but the hold was lifted after further investigation attributed the finding to the underlying disease rather than the drug [29].

Overall validation: High for PBC (FDA-approved with Phase 3 data).

Comparison to saroglitazar: Seladelpar is the most direct competitor to saroglitazar in the PBC space. It has the advantage of FDA approval and a higher composite biochemical response rate in Phase 3. Saroglitazar has the advantage of broader metabolic effects (lipid lowering, insulin sensitization) and approval for NASH and diabetic dyslipidemia, making it a more versatile compound for patients with overlapping metabolic and cholestatic liver disease. The two compounds target different PPAR subtypes (delta versus alpha/gamma), and future research may evaluate combination therapy.

12.5 Pemafibrate

Mechanism: Selective PPARalpha modulator (SPPARMalpha). Developed by Kowa Pharmaceuticals. Pemafibrate differs from classical fibrates (fenofibrate, bezafibrate) in its selective modulation of PPARalpha gene targets, potentially avoiding some fibrate-class adverse events.

Development trajectory: Pemafibrate is approved in Japan for hypertriglyceridemia. The Phase 3 PROMINENT trial (Pradhan et al. 2022) in 10,497 patients with type 2 diabetes, mild to moderate hypertriglyceridemia, and low HDL cholesterol evaluated pemafibrate 0.2 mg twice daily versus placebo for cardiovascular event reduction over a median 3.4 years of follow-up. Despite effective triglyceride reduction (26.2 percent versus placebo), the trial did not demonstrate reduction in cardiovascular events (hazard ratio 1.03) [30].

Novelty: Moderate. Selective PPARalpha modulation is an incremental advance over classical fibrate pharmacology.

Effect size: Triglyceride reduction of 26 percent (PROMINENT trial), lower than the 40 to 50 percent observed with fenofibrate and saroglitazar. No glycemic effect.

Promising potential: Low to moderate. The negative cardiovascular outcome in PROMINENT has substantially reduced enthusiasm for PPARalpha-selective strategies as cardiovascular risk reduction agents. The compound retains a role as a triglyceride-lowering agent in patients with severe hypertriglyceridemia (pancreatitis prevention).

Side-effect profile: Generally well tolerated. Renal adverse events were less frequent than with fenofibrate (no serum creatinine elevation). Hepatic adverse events were infrequent [30].

Overall validation: Moderate. Approved in Japan. Phase 3 negative for cardiovascular outcome despite effective lipid modification.

Comparison to saroglitazar: Pemafibrate is a more selective PPARalpha modulator than saroglitazar but lacks the PPARGamma-mediated insulin sensitization, anti-inflammatory, and antifibrotic effects. The PROMINENT trial outcome suggests that PPARalpha-selective triglyceride reduction alone is insufficient for cardiovascular event prevention, indirectly supporting the rationale for the dual PPARalpha/gamma approach of saroglitazar, which addresses both lipid and insulin-resistance pathways. Saroglitazar has the additional advantage of demonstrated efficacy in NASH and PBC, indications for which pemafibrate has not been evaluated.

12.6 Comparator summary

The five compounds occupy distinct positions in the PPAR agonist pharmacology space. **Fenofibrate** is the established PPARalpha-selective reference compound with extensive clinical experience but limited efficacy in NASH and no glycemic benefit. **Pioglitazone** is the established PPARGgamma-selective reference compound with the strongest NASH efficacy data but significant tolerability limitations. **Elafibranor** is a PPARalpha/delta dual agonist FDA-approved for PBC but with a failed NASH program. **Seladelpar** is a PPARDelta-selective agonist FDA-approved for PBC with strong efficacy data. **Pemafibrate** is a selective PPARalpha modulator with effective triglyceride reduction but a negative cardiovascular outcome trial.

Saroglitazar occupies a unique position in this comparator landscape: it is the only compound with dual PPARalpha/gamma agonism that has achieved and maintained marketing authorization; the only compound approved for both diabetic dyslipidemia and NASH (in India); the only compound with demonstrated efficacy across diabetic dyslipidemia, NASH, and PBC in published clinical trials; and the compound with the most favorable tolerability profile among the dual and selective PPAR agonists that have reached advanced clinical development. Its principal limitations are the absence of US FDA approval (anticipated for PBC in 2026), the smaller scale of its NASH clinical evidence base relative to pioglitazone, and the competition from recently FDA-approved PBC therapies (elafibranor, seladelpar) in the cholestatic liver disease space. Investigators considering saroglitazar for metabolic liver disease research should weigh its dual-mechanism versatility and favorable tolerability against the deeper Western clinical evidence bases of the comparator compounds.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Saroglitazar is approved in India for diabetic dyslipidemia and non-cirrhotic NASH, and in Mexico. It is not approved by the United States Food and Drug Administration. Regulatory submission for primary biliary cholangitis in the United States is anticipated in 2026. Investigators should consult their local regulatory authority before any human research application.