SAROGLITAZAR – FIRST NCE DISCOVERED AND DEVELOPED IN INDIA TO REACH THE MARKET

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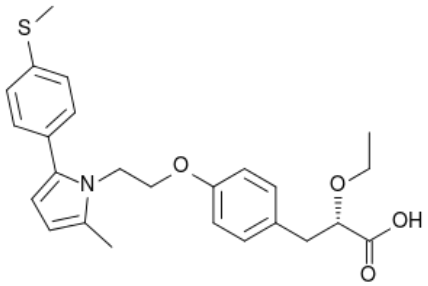
Zydus Cadila announced on June 5 2013 the approval by the Drug Controller General of India (DCGI) of Saroglitazar (ZYH1), or Lipaglyn™. The drug has been approved for launch in India for the treatment of diabetic dyslipidemia or hypertriglyceridemia in patients with type II diabetes not controlled by statins alone [1] .

Lipaglyn™ is the first glitazar to be approved in the world, and is the first NCE discovered and developed indigenously by an Indian company. The drug originates from a research program initiated at Zydus Cadila in 2000, and an IND submission in 2004 after extensive structure-activity relationship studies and preclinical characterization.

The compound belongs to the class of 'glitazars', dual peroxisome proliferator-activated receptor (PPAR) agonists with affinity towards both PPARα and PPARγ [2] [3]. According to Zydus Cadila [1], Saroglitazar has a predominant affinity for the PPARα isoform, and a moderate affinity for PPARγ, and has shown beneficial effects on lipids and glycemic controls without side effects. At a dose of 4 mg once daily, it reduces triglycerides and LDL cholesterol, it increases HDL cholesterol, and also shows a reduction in Fasting Plasma Glucose and glycosylated hemoglobin.

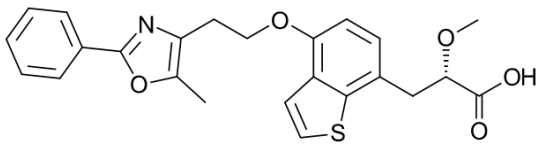
Chemical structure of Saroglitazar



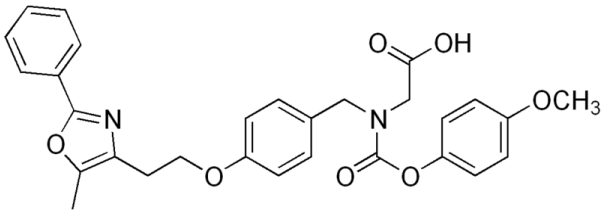
Saroglitazar, or (2S)-2-ethoxy-3-[4-(2-(2-methyl-5-[4-(methylsulfanyl)phenyl]-1H-pyrrol-1-yl)ethoxy) phenyl]propanoic acid, has been described in patent application WO 03/009841 A1, with a priority date of July 26, 2001, for its Indian patent application (711/MUM/2001).

The class of ‘glitazars’ also includes compounds such as:

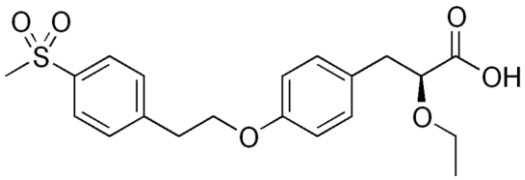
- Hoffmann-La Roche’s Aleglitazar (R1439), currently in Ph III trials [4]



- Bristol-Myers Squibb’s Muraglitazar (BMS-298585), which had completed Ph III clinical trials, but was discontinued in 2006



- AstraZeneca’s Tesaglitazar, also discontinued after Ph III trials in 2007



With 20 discovery research programs and a biosimilar pipeline, Zydus Cadila’s current NCE R&D pipeline, largely focused on diabetes and metabolic disorders, includes six compounds in Ph I and Ph II clinical stages [5].

Table: Zydus Cadila NCE pipeline

Project	Target	Indication	Status
ZYH7	PPARα agonist	Dyslipidemia	Ph II
ZYD1	GLP-1 agonist	Diabetes, obesity	Ph I
ZYOG1	Oral GLP-1 agonist	Diabetes, obesity	Ph I
ZYGK1	Glucokinase activator	Diabetes	Ph I
ZYG19	GPR-119 agonist	Diabetes	Ph I
ZYPH0907	Oral PTH agonist	Osteoporosis	Ph I

Additional Zydus Cadila compounds had progressed into clinical studies, but have been abandoned, such as:

- ZYI1, a multi-modal compound for the treatment of pain,
- ZYO1, a CB-1 antagonist for the treatment of obesity and diabetes
- ZYH2, another dual PPARα/PPARγ agonist for diabetes
- ZYT1, a Thyroid hormone receptor beta agonist for the treatment of dyslipidemia

Zydus Cadila invests over 7% of its turnover in research. The group employs over 15,000 people worldwide, and at the group's state-of-the-art research arm, the Zydus Research Centre, located in Ahmedabad, over 400 research scientists are engaged in NCE research alone [1].

Bibliography:

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[3] D. K. Nevin, D. Fayne and D. G. Lloyd, "Rational targeting of peroxysome proliferating activated receptor subtypes," *Current Medicinal Chemistry,* vol. 18, no. 36, pp. 5598-5623, 2011.

[4] Hoffmann-La Roche, 2013. [Online]. Available: http://www.roche.com/research_and_development/r_d_overview/pharmaceuticals/r_d_metabolism.htm.

[5] Zydus Cadila, 2013. [Online]. Available: http://www.zyduscadila.com/discovery.html.

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More information on drug discovery in India is available from:

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