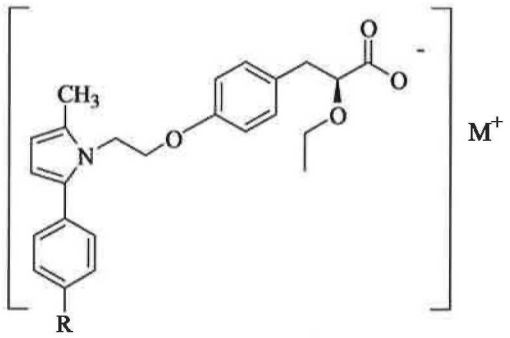



for reduction and removal of lipid accumulated in the liver cells (hepatocytes), required for treating and preventing certain diseases and conditions related to nonalcoholic fatty liver disease (NAFLD) including fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), and cirrhosis (advanced scarring of the liver) in patient in need of such treatment.

In another embodiment the present invention provides a method and a formulation comprising an effective amount of compound of Formula (I) for treating nonalcoholic fatty liver disease (NAFLD) including fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), and cirrhosis (advanced scarring of the liver).

The method comprises administering to a subject an effective amount of a compound of formula (I) as a pharmaceutical formulation, as disclosed hereinafter including pharmaceutically acceptable salts of the compound of formula (I).

In yet another embodiments the invention further provides a pharmaceutical composition containing effective amount of compound of formula (I) suitable for treatment of nonalcoholic fatty liver disease (NAFLD) including fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), and cirrhosis (advanced scarring of the liver).

In another embodiment the present invention provides a method of treating alcoholic steatohepatitis in a subject, comprising administering to the subject an effective amount of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof as a suitable pharmaceutically acceptable composition.

In another embodiment the present invention provides a method of treating liver failure in a subject, comprising administering to the subject an effective amount of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof.

The above and other embodiments of the present invention are disclosed further hereinafter.

**Description of the Figures:**

Figure 1: Effect of ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe on ALT in PP population

Figure 2: Effect of ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe on liver function test in Safety Population

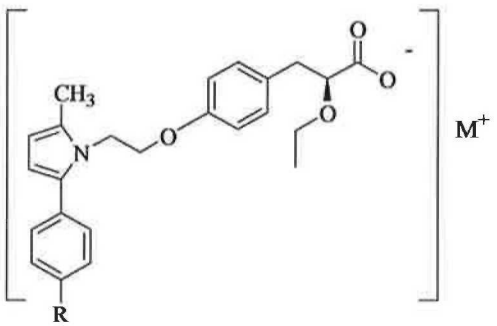
Figure 3: Effect of ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe on C-Peptide and HOMA Function in PP population

Figure 4: Effect of ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe on Triglycerides in PP population

**Detailed Description of the Invention**

The present invention describes a pharmaceutical composition for reduction and removal of lipid accumulated in the liver cells (hepatocytes), required for treating and preventing certain diseases and conditions in subject suffering from nonalcoholic fatty liver disease (NAFLD) including fatty liver (steatosis), nonalcoholic steatohepatitis (NASH), and cirrhosis (advanced scarring of the liver) and methods for ameliorating and/or treating such disease conditions.

The formulation comprises compound of formula (I) and the method comprises administering to a subject in need thereof an effective amount of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof.




(I)

wherein 'R' is selected from hydroxy, hydroxyalkyl, acyl, alkoxy, alkylthio, thioalkyl, aryloxy, arylthio and $M^+$ represents suitable metal cations such as $Na^+$, $K^+$, $Ca^{+2}$, $Mg^{+2}$ and the like.

**Definitions and Abbreviations**

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following

Meanings:

"Patient" includes both human and animals. "Mammal" means humans and other mammalian animals.

A "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats,

optimum dose based on the patient profile, the severity of disease, the presence of secondary medicines and the like.

The compound of formula (I), when R is -SMe and M+ is Mg, ~~is commercially known as Saroglitazar. This compound (Saroglitazar)~~ is dosed to patients in need thereof for the treatment of one or more of the diseases described above as per the following general protocol:

**Study design and Protocol:**

**Title of the Study** - "A prospective, multi-centric, open-label, single arm study to evaluate the safety and efficacy of 4 mg of ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe in a pharmaceutical composition as described above in Non-alcoholic steatohepatitis."

**Objectives:**

To evaluate the safety and efficacy of 4mg of ~~compound of Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe in Non-alcoholic steatohepatitis (NASH).

**The following effficacy parameters were measured:**

Primary Efficacy (Time frame 6 and 12 weeks):

1. Change in alanine aminotransferase (ALT) from baseline

Secondary Efficacy (Time frame 6 and 12 weeks):

- Sustained reduction in ALT level.
- C-peptide test for homeostasis model assessment (HOMA) beta and HOMA IR
- Triglyceride (TG)

**Criteria for Safety:**

1. General and Systemic Clinical Examination: Cardiovascular system (CVS), respiratory system (RS), gastro-intestinal system (GIS), central nervous system (CNS) etc.

2. Laboratory Investigations: Complete blood count (CBC), aspartate aminotransferase(AST), ALT, alkaline phosphatase (ALP), serum bilirubin, γ-glutamyl transpeptidase (GGT), Serum proteins, blood urea nitrogen (BUN), Serum creatinine, creatinine phosphokinase (CPK), fasting plasma glucose (FPG).

3. Frequency and severity of adverse events (AEs) for all subjects enrolled were recorded. All AEs, were classified using

- causality
- severity
- seriousness

**Methodology:**

It is an interventional, single arm, safety and efficacy study to explore effect of ~~compound of Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe suitably formulated as described above, on NASH.

Subjects was diagnosed by biopsy as suffering from NASH in last one year and willing to participate in study were invited for screening programme for inclusion in the study.

Subjects satisfying inclusion exclusion criteria will be enrolled in the study.

All subjects were given suitable formulation of ~~compound of Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe 4 mg for 12 weeks. Lifestyle modification was continued as before the study. Patient was monitored for safety and efficacy of ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe.

**Study Schedules:**

Informed consent was obtained before any trial related activity.

- **Visit 1, Screening Visit/ Enrolment [Week -1 to 0]**

Subjects were screened for the inclusion and exclusion criteria and those qualifying were invited to participate in the study. Clinical evaluation was done for baseline characteristics and anthropometry

After Clinical evaluations, all baseline safety and efficacy parameters were recorded as per Table (I) given below. All laboratory investigations were carried out after overnight fasting.

During the 12 week program, a designated person from the centre could interview the subjects for his/her general health, telephonically.

Enrolled Subjects would receive the study medication for next two weeks.

Patients were advised to follow same lifestyle modifications during study period as before the study.

- **Visit 2, [Week 2]**

Subjects were clinically examined and given the study medications for four weeks and also safety parameters were assessed as per Table (I)given below.

- **Visit 3 [Week 6]**

Subjects were clinically examined and given the study medications for next 6 weeks.

Safety and efficacy parameters were assessed as per Table (I) given below.

- **Visit 4 [Week 12]**

Subjects were clinically examined and safety and efficacy parameters were

- Other cause of chronic liver disease [autoimmune, primary biliary cirrhosis, hepatitis B virus (HBV), Wilson, alpha-1-antitrypsin deficit, hemochromatosis etc.] i.e. Antinuclear antibodies (ANA) > 1:160, Anti-smooth muscle Ab positive >1:160 , Serum hepatitis B surface antigen (HepBsAg) positive, Serum hepatitis C antibody (HepC Ab) positive, transferrin saturation > 45%

**Results**

Subjects were screened for inclusion in the study after obtaining informed consent, out of which 32 subjects were enrolled into the study. Out of these 32 subjects, 29 subjects completed the study.

The effect of ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe at week 12 on various parameters of liver function is as below.

- There was statistically significant reduction in the ALT levels from baseline in ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe 4 mg treatment group in the PP population at visit 3 and visit 4. (Figure 1)
- There was sustained reduction in ALT levels 63.16% and 78.95% of patients at visit 3 and visit 4 respectively as per PP.
- ~~Saroglitazar~~ Magnesium salt of compound of formula (I) wherein R is –SMe showed a statistical significant decrease in the Aspartate Transaminase, gamma-glutamyl transpeptidase and alkaline phosphatase at Week 3 and at Week 4 in the Safety Population. (Figure 2)
- There was a non-significant change in the C peptide levels in ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe 4 mg at 6 and 12 weeks as per PP analysis and non-statistically significant reduction in HOMA – Beta cell function, HOMA – Insulin Resistance. (Figure 3)
- Baseline TG < 150 mg/dl - There was decrease in triglyceride in ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe 4 mg at week 12 as compared to baseline but it was not statistically significant in the PP population.(Figure 4)
- Baseline TG ≥ 150 mg/dl – While decrease was observed in serum triglycerides at week 6 and 12 as compared to baseline but it was not statistically significant in ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe 4 mg in PP population. (Figure 4)

**Safety Conclusion:**

Overall, ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe 4 mg was safe and well tolerated.

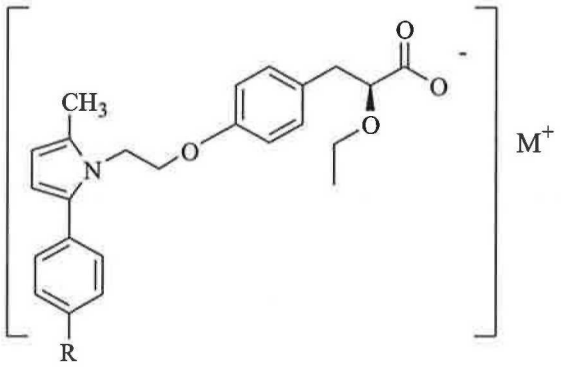
- There were no deaths or SAEs reported in the ~~Saroglitazar~~ magnesium salt of compound of formula (I) whercin R is –SMe 4 mg treatment arm.
- The overall incidence of AEs was Nil.
- There were no persistent changes from baseline in various laboratory parameters. Few events of raised creatinine and five events of raised CPK value were reported during the study. These events were mild and none of these events were considered clinically significant by the investigator.
- There was no significant change in weight in ~~Saroglitazar~~ magnesium salt of compound of formula (I) wherein R is –SMe 4 mg group in NASH patients at visit 2, 3 and 4 visits compared to baseline.

Thus, the compounds of the present invention and the pharmaceutical composition as described in the specification are suitable for reduction and removal of lipid accumulated in the liver cells (hepatocytes) for the treatment of Nonalcoholic fatty liver disease (NAFLD) which refers to a wide spectrum of liver diseases ranging from simple fatty liver (steatosis) to nonalcoholic steatohepatitis (NASH).

**Claims:**

1. The use of ~~A~~a pharmaceutical composition in the manufacture of a medicament for the treatment of nonalcoholic fatty liver disease (NAFLD), wherein the pharmaceutical composition comprising

   (a) the pharmaceutically active substance of Formula (I);




   wherein 'R' is selected from hydroxy, hydroxyalkyl, acyl, alkoxy, alkylthio, thioalkyl, aryloxy, arylthio and $M^+$ represents suitable metal cations selected from Na+, K+, Ca+2, Mg+2

   (b) suitable additives

   (c) a suitable stabilizer;

   (d) optionally with one or more pharmaceutically acceptable excipients.

   ~~for the treatment of nonalcoholic fatty liver disease (NAFLD).~~

2. The use according to~~pharmaceutical composition as claimed in~~ claim 1, ~~used~~wherein the use of the pharmaceutical composition is for the reduction and removal of lipid accumulated in the liver cells (hepatocytes).

3. The ~~pharmaceutical composition of~~use according to claims 1 ~~&~~ or 2, wherein the use of the pharmaceutical composition is for the prevention and/or reducing/ameliorating the conditions associated with non-alcoholic fatty liver disease (NAFLD) including fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), and cirrhosis (advanced scarring of the liver)

4. The ~~pharmaceutical composition of~~use according to claim 3, wherein the disease condition is fatty liver (steatosis).

5. The ~~pharmaceutical composition of~~ use according to claim 3, wherein the disease condition is non-alcoholic steatohepatitis (NASH).
6. The ~~pharmaceutical composition of~~use according to claim 3, wherein the disease condition is cirrhosis.
7. The ~~pharmaceutical composition as claimed in~~use according to claim 1, wherein the suitable stabilizer is selected from antioxidants or chelating agents.
8. The pharmaceutical composition as claimed inuse according to claim 7, wherein the suitable antioxidants are selected from citric acid, alpha tocopherol, sodium sulphite, sodium metabisulphite, butylated hydroxy anisole (BHA), BHT (2,6-di-tert-butyl-4-methylphenol), monothioglycerol, Vitamin C (ascorbic acid).
9. The ~~pharmaceutical composition as claimed in~~use according to claim 7, wherein the suitable chelating agents are selected from Disodium EDTA, citric acid and or its salts, maleic acid, chlorambutol, chlorhexidine.
10. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein pharmaceutically active substance of Formula (I) is used in the range of 0.5 mg to 5 g.
11. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable excipients are selected from solubilizers, diluents, fillers, disintegrants, binder, lubricants, glidants, wetting agents and solvents.
12. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable additives are selected from sodium benzoate, sodium hydroxide, sodium sulfite and sodium carbonate.
13. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable binders are selected from acacia alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methyl cellulose, povidone and pregelatinized starch, combinations thereof; poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC F68, PLURONIC F127), collagen, albumin, celluloses in nonaqueous solvents, and the like or their suitable combinations; poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone).

14. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable glidants are selected from glicolloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, corn starch and talc.

15. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable glidants are selected from calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate.

16. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable lubricants are selected from calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate.

17. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable disintegrant are selected from starches such as corn starch, potato starch, pre-gelatinized and modified starches, sweeteners, clays, microcrystalline cellulose, carsium, alginates, sodium starch glycolate, gums, guar, locust bean, karaya, pectin, tragacanth.

18. The ~~pharmaceutical composition as claimed in~~use according to any of the preceding claims, wherein the suitable wetting agent are selected from poloxamers, gelatin, casein, Glycerol mono-oleate, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol,sodium lauryl sulphate, sodium dodecyl sulfate, salts of bile acids, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxy methylcellulose, sodium methyl cellulose, hydroxyethyl cellulose, hydroxylpropyl cellulose, hydroxy propyl methyl cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and poly vinyl pyrrolidone.

19. The ~~composition as claimed in~~use according to any of the preceding claims, wherein the composition is formulated in tablet or capsule forms.

20. The ~~composition as claimed in~~use according to any of the preceding claims, wherein the pH is maintained in the range of 6 to 10.

21. The ~~compound as claimed in~~use according to claim 1, wherein R is –SMe and $M^{+}$ is $Mg^{+2}$.

22. A method of treating and/or ameliorating nonalcoholic fatty liver disease (NAFLD) by treating a patient the composition as claimed in any preceding claim.

23. The method as claimed in claim 22, wherein the disease condition includes fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), and cirrhosis of the liver.

24. The method as claimed in claim 22 wherein the composition comprises compound of formula (I) wherein R is –SMe and $M^{+}$ is $Mg^{+2}$.

25. Use of the composition of claim 1 for the treatment of non-alcoholic fatty liver disease (NAFLD).