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Lobeglitazone and Next-Generation PPAR-γ Modulators: Therapeutic Potential in Type 2 Diabetes Mellitus, NAFLD, and Metabolic Syndrome

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Abstract
Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive β-cell dysfunction. Thiazolidinediones (TZDs) are a unique class of oral antidiabetic agents that improve insulin sensitivity through activation of peroxisome proliferator-activated receptor-gamma (PPAR-γ). Lobeglitazone is a novel TZD developed to overcome the limitations associated with earlier TZDs such as rosiglitazone and pioglitazone. It exhibits potent glucose-lowering effects, improved lipid metabolism, and favorable safety outcomes at lower therapeutic doses. This review summarizes the chemistry, mechanism of action, pharmacokinetics, pharmacodynamics, clinical efficacy, safety profile, and future therapeutic prospects of lobeglitazone in the management of T2DM.

Keywords: Lobeglitazone, Type 2 Diabetes Mellitus, Thiazolidinedione, PPAR-γ agonist, Insulin resistance, Antidiabetic agents.

I. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin resistance and progressive impairment of pancreatic β-cell function. The prevalence of T2DM has increased dramatically over the past two decades owing to sedentary lifestyles, obesity, population aging, and dietary transitions. In addition to hyperglycemia, patients with T2DM frequently exhibit dyslipidemia, hypertension, endothelial dysfunction, and increased cardiovascular risk.Insulin resistance is considered a fundamental defect in the pathogenesis of T2DM. Consequently, therapeutic strategies targeting insulin sensitivity have attracted considerable attention. Among available oral antidiabetic agents, thiazolidinediones (TZDs) directly improve insulin sensitivity through activation of the nuclear receptor PPAR-γ. Activation of this receptor regulates glucose homeostasis, adipocyte differentiation, lipid metabolism, and inflammatory signaling pathways. Despite their efficacy, earlier TZDs such as rosiglitazone and pioglitazone have been associated with several adverse effects, including fluid retention, weight gain, edema, heart failure risk, and concerns regarding long-term safety. These limitations stimulated the development of newer PPAR-γ modulators with improved therapeutic profiles.

Lobeglitazone is a novel TZD developed through structural modification of rosiglitazone. The incorporation of a p-methoxyphenoxy group into its molecular structure enhances receptor-binding affinity and pharmacological potency. Experimental studies have demonstrated that lobeglitazone exhibits substantially higher affinity for PPAR-γ than earlier TZDs while maintaining effective glycemic control at lower doses. The drug has shown promising effects on fasting plasma glucose, glycated hemoglobin (HbA1c), insulin sensitivity, lipid metabolism, and hepatic steatosis. Beyond glucose lowering, emerging evidence suggests that lobeglitazone may offer therapeutic benefits in non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, diabetic nephropathy, and cardiovascular risk management. These pleiotropic effects have generated increasing scientific interest in evaluating its role as a next-generation insulin sensitizer.

The present review aims to critically evaluate the pharmacological characteristics, clinical evidence, therapeutic applications, safety considerations, and future prospects of lobeglitazone in the management of T2DM and associated metabolic disorders

II. Methodology

2.1 Review Design

This review was conducted to critically evaluate the pharmacological, pharmacokinetic, pharmacodynamic, clinical, and therapeutic aspects of lobeglitazone in the management of Type 2 Diabetes Mellitus (T2DM) and associated metabolic disorders. A comprehensive narrative review

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approach was adopted to summarize available evidence regarding the efficacy, safety, and future therapeutic potential of lobeglitazone.

2.2 Literature Search Strategy

A systematic literature search was performed using electronic databases including PubMed, Scopus, Web of Science, Science Direct, Google Scholar, Springer Link, and Wiley Online Library. Relevant articles published between 2013 and 2026 were retrieved. The search strategy utilized combinations of Medical Subject Headings (MeSH) terms and keywords related to lobeglitazone and diabetes management

III. Drug Profile and Chemistry of Lobeglitazone

3.1 Drug Profile of Lobeglitazone

Lobeglitazone is a novel thiazolidinedione (TZD) class oral antidiabetic drug developed for the treatment of Type 2 Diabetes Mellitus (T2DM). It was developed by Chong Kun Dang Pharmaceutical Corporation, South Korea, and approved in 2013 for clinical use. The drug is marketed under the brand name Duvie® and is prescribed primarily to improve glycemic control in patients with insulin resistance. Lobeglitazone belongs to the class of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) agonists, which enhance insulin sensitivity and regulate glucose and lipid metabolism. It was developed to overcome the limitations of earlier TZDs such as rosiglitazone and pioglitazone, which were associated with adverse cardiovascular and safety concerns. Lobeglitazone demonstrates potent glucose-lowering efficacy at a lower therapeutic dose of 0.5 mg once daily and has shown beneficial effects on lipid metabolism, hepatic steatosis, and insulin resistance.

Drug Profile Table

Parameter	Details
Generic Name	Lobeglitazone
Brand Name	Duvie®, LOBG
Drug Class	Thiazolidinedione (TZD)
Therapeutic Class	Oral Antidiabetic Agent
Mechanism	PPAR-γ Agonist
Molecular Formula	$C_{24}H_{24}N_4O_5S$
Molecular Weight	480.54 g/mol
Route of Administration	Oral
Recommended Dose	0.5 mg Once Daily
Indication	Type 2 Diabetes Mellitus
Developer	Chong Kun Dang Pharmaceutical Corporation
Approval Year	2013

3.2 Chemistry of Lobeglitazone

Lobeglitazone is a synthetic thiazolidinedione derivative containing a 2,4-thiazolidinedione ring, which is considered the pharmacophore responsible for antidiabetic activity. The chemical structure consists of a thiazolidinedione nucleus linked to a substituted pyrimidine moiety through an ethoxybenzyl-N-methylamino linker. The molecular formula of lobeglitazone is $C_{24}H_{24}N_4O_5S$. Its IUPAC chemical name is 5-[4-(2-{[6-(4-methoxyphenoxy)-pyrimidin-4-yl]-methyl-amino}-ethoxy)benzyl]-thiazolidine-2,4-dione hydrosulfate.

A key structural feature of lobeglitazone is the introduction of a p-methoxyphenoxy group at the fourth position of the pyrimidine ring. This modification distinguishes lobeglitazone from rosiglitazone and significantly enhances its interaction with the hydrophobic pocket of the PPAR-γ receptor. As a result, lobeglitazone exhibits approximately 12-fold higher binding affinity toward PPAR-γ compared with rosiglitazone and pioglitazone. This enhanced receptor affinity contributes to improved pharmacological efficacy at lower doses.

The p-methoxyphenoxy moiety extends into the third arm of the ligand-binding pocket of the PPAR-γ receptor and forms additional hydrophobic interactions with amino acid residues such as Ile249, Leu255, Ile281, Ile341, and Met348. Furthermore, weak hydrogen bonding interactions occur between the ether oxygen of the p-methoxyphenoxy group and Arg280 residue of the receptor. These molecular interactions stabilize the drug-receptor complex and account for its superior biological activity.

Chemical Structure of Lobeglitazone
Molecular Formula: $C_{24}H_{24}N_4O_5S$
Molecular Weight: 480.54 g/mol

IV. Pharmacodynamics of Lobeglitazone

Lobeglitazone is a novel thiazolidinedione (TZD) that acts as a potent and selective Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) agonist. PPAR-γ is a nuclear transcription factor that regulates genes involved in glucose metabolism, lipid metabolism, adipocyte differentiation, and insulin sensitivity. Activation of PPAR-γ by lobeglitazone enhances insulin responsiveness in peripheral tissues,

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thereby improving glycemic control in patients with Type 2 Diabetes Mellitus (T2DM).

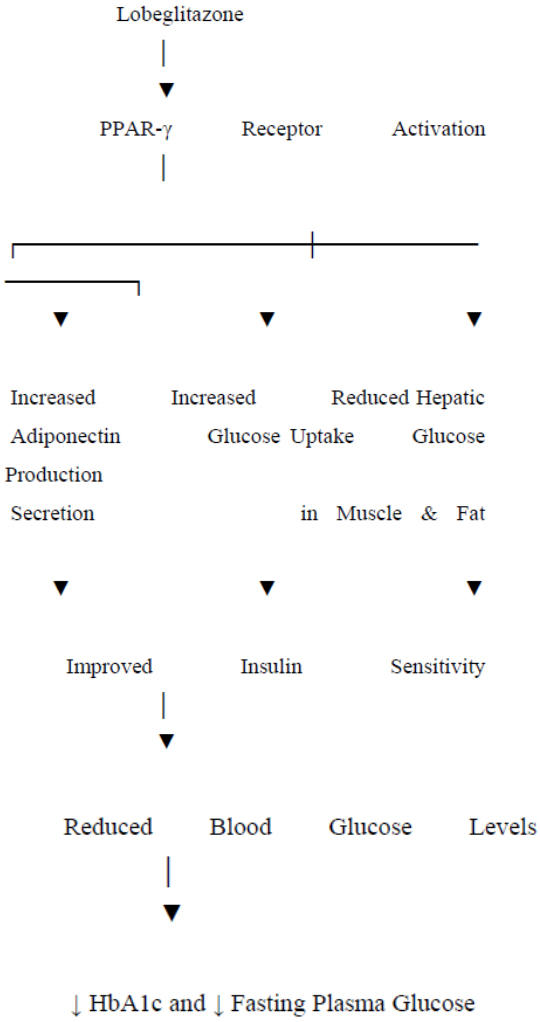
A unique structural modification in lobeglitazone, namely the incorporation of a p-methoxyphenoxy group**,** results in approximately 12-fold greater binding affinity toward the PPAR-γ receptor compared with rosiglitazone and pioglitazone. This increased receptor affinity allows effective glucose control at a lower therapeutic dose of 0.5 mg daily.

Upon activation of PPAR-γ receptors, lobeglitazone promotes glucose uptake in skeletal muscles and adipose tissues by increasing the expression of glucose transporter proteins. Simultaneously, it suppresses hepatic gluconeogenesis, leading to reduced glucose production by the liver. These actions collectively improve insulin sensitivity and decrease blood glucose concentrations.

In addition to its glucose-lowering effects, lobeglitazone exerts beneficial effects on lipid metabolism. It decreases plasma triglyceride levels, reduces free fatty acid concentrations, and increases high-density lipoprotein (HDL) cholesterol levels. The drug also exhibits anti-inflammatory properties through modulation of adipokines such as adiponectin and adipsin, contributing to improved metabolic homeostasis.

Recent studies have demonstrated that lobeglitazone may reduce hepatic fat accumulation and improve non-alcoholic fatty liver disease (NAFLD), indicating therapeutic benefits beyond glycemic control. Thus, the pharmacodynamic profile of lobeglitazone encompasses insulin sensitization, glucose regulation, lipid modulation, and anti-inflammatory activity.

Mechanism of Action



V. Pharmacokinetics of Lobeglitazone

The pharmacokinetic profile of lobeglitazone supports its once-daily administration and contributes to its clinical efficacy. Following oral administration, lobeglitazone is rapidly absorbed from the gastrointestinal tract and reaches therapeutic plasma concentrations at relatively low doses.

Absorption

Lobeglitazone is administered orally at a recommended dose of 0.5 mg once daily**.** The drug exhibits good oral absorption and demonstrates dose-proportional pharmacokinetics. Food intake has minimal influence on its absorption. Although a high-fat meal may slightly increase systemic exposure, the effect is not clinically significant, allowing administration with or without food.

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Distribution
After absorption, lobeglitazone is extensively distributed throughout the body. It demonstrates high plasma protein binding and preferential distribution to insulin-sensitive tissues such as adipose tissue, skeletal muscle, and liver. The drug's lipophilic nature facilitates penetration into target tissues where PPAR-γ receptors are abundantly expressed.

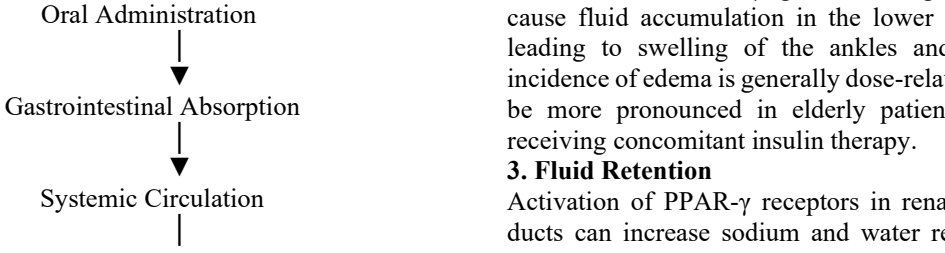
Metabolism
Lobeglitazone undergoes extensive hepatic metabolism. The liver converts the parent drug into several metabolites, among which M7 is considered an active metabolite contributing to the pharmacological effect. Hepatic metabolism plays a major role in determining the duration and intensity of drug action.

Elimination
The elimination of lobeglitazone occurs primarily through hepatic pathways, with metabolites being excreted via bile and feces. A smaller proportion is eliminated through the kidneys. The elimination profile supports sustained therapeutic plasma concentrations and permits once-daily dosing.

Drug–Drug Interactions
Pharmacokinetic studies have shown that lobeglitazone does not significantly alter the pharmacokinetics of metformin when administered concurrently. Similarly, co-administration with amlodipine does not produce clinically relevant pharmacokinetic interactions. Therefore, dose adjustment is generally not required when these medications are used together.

Special Pharmacokinetic Characteristics
- Effective at a low dose of 0.5 mg/day
- Minimal effect of food on absorption
- High tissue distribution
- Extensive hepatic metabolism
- Active metabolite formation (M7)
- Suitable for once-daily administration
- No significant interaction with metformin or amlodipine

Pharmacokinetic Flow Diagram



VI. Side Effects and Adverse Effects of Lobeglitazone

Introduction
Lobeglitazone is generally well tolerated and has demonstrated a favorable safety profile in clinical studies. However, similar to other thiazolidinediones (TZDs), its use may be associated with certain side effects and adverse reactions. Most adverse effects are related to fluid retention, weight gain, and changes in adipose tissue metabolism resulting from PPAR-γ activation. Although the incidence of severe adverse reactions appears lower than that reported for earlier TZDs, careful monitoring is recommended, particularly in patients with cardiovascular disease or heart failure.

Common Side Effects
1. Weight Gain
Weight gain is one of the most frequently reported side effects of lobeglitazone therapy. The increase in body weight is primarily attributed to improved adipocyte differentiation, increased fat storage in subcutaneous tissues, and fluid retention. Although weight gain is generally mild to moderate, patients should be advised regarding dietary control and regular physical activity.
2. Peripheral Edema
Peripheral edema is another common adverse effect associated with PPAR-γ agonists. Lobeglitazone may cause fluid accumulation in the lower extremities, leading to swelling of the ankles and feet. The incidence of edema is generally dose-related and may be more pronounced in elderly patients or those receiving concomitant insulin therapy.
3. Fluid Retention
Activation of PPAR-γ receptors in renal collecting ducts can increase sodium and water reabsorption,

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resulting in fluid retention. This effect may contribute to edema and increased body weight during treatment.

4. Increased Appetite

Some patients may experience increased appetite, which can indirectly contribute to weight gain during long-term therapy.

VII. Less Common Adverse Effects

1. Headache

Mild to moderate headache has been reported in some patients during clinical trials. The condition is generally transient and resolves without discontinuation of therapy.

2. Dizziness

Occasional dizziness may occur, particularly during the initiation phase of treatment. Patients should be advised to exercise caution when operating machinery or driving if symptoms occur.

3. Fatigue

Some individuals may experience fatigue or generalized weakness during treatment. These symptoms are usually mild and self-limiting.

4. Gastrointestinal Disturbances

Mild gastrointestinal complaints such as:

- Nausea
- Abdominal discomfort
- Dyspepsia
- Diarrhea

have been reported but occur infrequently.

Serious Adverse Effects

1. Congestive Heart Failure

Like other TZDs, lobeglitazone may exacerbate existing heart failure due to fluid retention. Patients with New York Heart Association (NYHA) Class III or IV heart failure should generally avoid TZD therapy.

2. Hepatic Dysfunction

Although significant hepatotoxicity has not been commonly reported with lobeglitazone, periodic monitoring of liver function tests is recommended, especially in patients with pre-existing liver disease.

3. Bone Fractures

Long-term use of TZDs has been associated with decreased bone mineral density and increased fracture risk, particularly in postmenopausal women. Although data specific to lobeglitazone remain limited, caution is advised during prolonged therapy.

4. Anemia

Mild reductions in hemoglobin and hematocrit may occur due to plasma volume expansion resulting from fluid retention.

Laboratory Abnormalities

Clinical studies have reported occasional changes in laboratory parameters including:

- Mild increase in body weight
- Mild elevation of liver enzymes
- Reduction in hemoglobin levels
- Changes in lipid profile
- Increased plasma volume

These abnormalities are generally mild and reversible.

Contraindications

Lobeglitazone should be used cautiously or avoided in:

- Severe heart failure (NYHA Class III–IV)
- Severe hepatic impairment
- Hypersensitivity to lobeglitazone or its components
- Pregnancy and lactation (unless clearly indicated)

Monitoring During Therapy

Patients receiving lobeglitazone should be monitored for:

- Body weight changes
- Peripheral edema
- Signs of heart failure
- Liver function tests (ALT, AST)
- Blood glucose and HbA1c levels
- Lipid profile
- Renal function (when clinically indicated)

Summary Table of Adverse Effects

Adverse Effect	Frequency	Severity
Weight Gain	Common	Mild–Moderate
Peripheral Edema	Common	Mild–Moderate
Fluid Retention	Common	Mild–Moderate
Headache	Uncommon	Mild
Dizziness	Uncommon	Mild
Fatigue	Uncommon	Mild
Gastrointestinal Disturbances	Uncommon	Mild
Congestive Heart Failure	Rare but Serious	Severe
Hepatic Dysfunction	Rare	Moderate
Bone Fracture Risk	Long-term Concern	Moderate
Anemia	Rare	Mild

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Advantages of Lobeglitazone Over Other Antidiabetic Drugs

Compared with Metformin

- Better improvement in insulin sensitivity.
- Beneficial effects on lipid metabolism.
- Useful in patients with marked insulin resistance.

Compared with Pioglitazone

- Lower therapeutic dose (0.5 mg vs 15–45 mg).
- Higher PPAR-γ binding affinity.
- Potentially lower incidence of edema and weight gain.
- Better receptor selectivity.

Compared with Rosiglitazone

- Improved cardiovascular safety profile.
- Superior receptor affinity.
- Better metabolic outcomes.

Compared with Sulfonylureas

- Minimal risk of hypoglycemia.
- Better long-term insulin sensitivity.
- Does not overstimulate pancreatic β-cells.

Compared with DPP-4 Inhibitors

- Greater effect on insulin resistance.
- Better triglyceride reduction.
- More pronounced metabolic benefits.

Compared with SGLT2 Inhibitors

- Stronger insulin-sensitizing action.
- Greater effect on adiponectin and lipid metabolism.
- Better efficacy in some patients with severe insulin resistance.

Limitations of Lobeglitazone

- May cause weight gain and edema.
- Not preferred in severe heart failure.
- Less cardiovascular outcome data compared with SGLT2 inhibitors and GLP-1 receptor agonists.
- Limited global clinical experience compared with metformin and pioglitazone.

Global Studies on Lobeglitazone

For your review article, you can include the following section under "Global Clinical Studies and Evidence of Lobeglitazone"**.**

VIII. Global Clinical Studies on Lobeglitazone

Although lobeglitazone was initially developed and approved in South Korea, its efficacy and safety have been evaluated through multiple multicenter clinical trials, observational studies, and meta-analyses. These studies have demonstrated significant improvements in glycemic control, insulin sensitivity, lipid metabolism, and cardiovascular outcomes in patients with Type 2 Diabetes Mellitus (T2DM).

8.1. Phase III Multicenter Monotherapy Trial (2014)

One of the earliest global clinical studies evaluated lobeglitazone as monotherapy in patients with T2DM. In this randomized, double-blind, placebo-controlled trial involving 173 patients, treatment with lobeglitazone 0.5 mg once daily for 24 weeks resulted in a significant reduction in HbA1c levels compared with placebo. Approximately 44% of patients achieved HbA1c levels below 7%, compared with only 12% in the placebo group. Significant improvements were also observed in fasting plasma glucose and lipid parameters.

8.3. Lobeglitazone as Add-on Therapy with Metformin

Several studies investigated lobeglitazone in combination with metformin. Results demonstrated significant reductions in HbA1c, fasting blood glucose, and insulin resistance without clinically relevant pharmacokinetic interactions. These findings support the use of lobeglitazone as an effective add-on therapy in patients inadequately controlled on metformin alone.

8.3. Phase III Triple-Therapy Study (2025)

A 52-week multicenter, randomized, placebo-controlled Phase III clinical trial evaluated lobeglitazone in combination with metformin and sitagliptin in 231 patients with inadequately controlled T2DM. Patients receiving lobeglitazone showed improvements in HbA1c, fasting plasma glucose, insulin resistance indices (HOMA-IR), β-cell function, and lipid profiles. The treatment was generally well tolerated and maintained long-term glycemic control.

8.4. Cardiovascular Outcome Study (2023)

A nationwide Korean study involving more than 70,000 patients with T2DM and ischemic stroke investigated the cardiovascular effects of lobeglitazone. The study reported that lobeglitazone therapy was associated with a significantly lower risk of recurrent stroke, myocardial infarction, and all-cause mortality. Importantly, the drug did not significantly increase the risk of heart failure, suggesting a favorable cardiovascular safety profile.

8.5. Effects on Non-Alcoholic Fatty Liver Disease (NAFLD)

Recent studies have highlighted the beneficial effects of lobeglitazone on hepatic steatosis and NAFLD. Improvement in liver enzymes, hepatic fat accumulation, and insulin resistance has been

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observed, indicating potential therapeutic utility beyond glycemic control.

8.6. Systematic Review and Meta-analysis (2023)

A systematic review and meta-analysis evaluating randomized controlled trials compared lobeglitazone with standard antidiabetic therapy. The analysis demonstrated comparable reductions in HbA1c and fasting blood glucose, with a lower risk of hypoglycemia and a safety profile similar to standard treatments. The authors concluded that lobeglitazone is an effective and well-tolerated therapeutic option for T2DM management.

IX. Summary of Lobeglitazone

Lobeglitazone is a novel third-generation thiazolidinedione (TZD) and a potent PPAR-γ agonist developed for the treatment of Type 2 Diabetes Mellitus (T2DM). It was developed by Chong Kun Dang Pharmaceutical Corporation and approved in South Korea in 2013. The drug is administered orally at a low dose of **0.5** mg once daily and exhibits approximately 12-fold higher affinity for PPAR-γ receptors compared with earlier TZDs such as pioglitazone and rosiglitazone.

Lobeglitazone improves insulin sensitivity by enhancing glucose uptake in skeletal muscle and adipose tissue while reducing hepatic glucose production. Through activation of PPAR-γ receptors, it effectively lowers fasting plasma glucose and HbA1c levels and improves lipid metabolism. Clinical studies have demonstrated significant reductions in triglycerides and increases in HDL cholesterol, making it beneficial in patients with insulin resistance and metabolic syndrome.

Pharmacokinetically, lobeglitazone is well absorbed after oral administration, extensively distributed to insulin-sensitive tissues, and primarily metabolized in the liver to active metabolites. It exhibits minimal food effects and no clinically significant interactions with metformin or amlodipine, supporting convenient once-daily dosing.

In addition to glycemic control, lobeglitazone has shown promising benefits in non-alcoholic fatty liver disease (NAFLD), dyslipidemia, and cardiovascular risk management. Global clinical studies have demonstrated its efficacy both as monotherapy and as add-on therapy with metformin and other antidiabetic agents.

The most commonly reported adverse effects include weight gain, peripheral edema, and fluid retention, which are characteristic of the TZD class. However, available evidence suggests that lobeglitazone possesses a favorable safety profile compared with older TZDs.

Overall, lobeglitazone represents a promising next-generation insulin sensitizer that combines potent glucose-lowering activity, improved lipid regulation, and potential benefits in metabolic disorders. Its unique pharmacological profile and emerging clinical evidence support its growing role in the management of Type 2 Diabetes Mellitus and associated metabolic complications.

X. Conclusion

Lobeglitazone is a novel and potent third-generation thiazolidinedione that has emerged as a promising therapeutic option for the management of Type 2 Diabetes Mellitus (T2DM). Through selective activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ), lobeglitazone effectively improves insulin sensitivity, enhances peripheral glucose uptake, and reduces hepatic glucose production, thereby addressing one of the fundamental pathophysiological defects of T2DM. Its unique structural modification, involving the incorporation of a p-methoxyphenoxy group, provides significantly greater receptor-binding affinity and allows effective glycemic control at a lower therapeutic dose compared with conventional TZDs. Clinical studies have consistently demonstrated that lobeglitazone significantly reduces fasting plasma glucose and HbA1c levels while improving lipid metabolism and insulin resistance. Beyond glycemic control, the drug has shown beneficial effects on dyslipidemia, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, and cardiovascular risk factors, highlighting its pleiotropic therapeutic potential. Pharmacokinetic studies further support its clinical utility by demonstrating favorable absorption, predictable pharmacokinetics, extensive tissue distribution, minimal food effects, and limited drug–drug interactions.

Although adverse effects such as weight gain, edema, and fluid retention remain concerns, the overall safety profile of lobeglitazone appears favorable when compared with earlier members of the TZD class. Nevertheless, long-term studies evaluating cardiovascular outcomes, safety in special populations, and real-world effectiveness are still required.

In conclusion, lobeglitazone represents an important advancement in insulin-sensitizing therapy and offers a valuable treatment option for patients with Type 2 Diabetes Mellitus, particularly those with significant insulin resistance and associated metabolic disorders. Future large-scale clinical trials and precision medicine approaches

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may further expand its therapeutic applications and establish its role in the comprehensive management of diabetes and metabolic diseases.

Future Perspective

Future research should focus on long-term cardiovascular safety, pharmacogenomic profiling, combination therapy with SGLT2 inhibitors and GLP-1 receptor agonists, and the role of lobeglitazone in the management of NAFLD and metabolic syndrome. Such studies may help establish lobeglitazone as a key component of next-generation antidiabetic therapy and broaden its clinical applications beyond glycemic control.

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