Gemigliptin (Zemiglo): Newer Dipeptidyl Peptidase Inhibitors for Type 2 Diabetes Mellitus.

The optimal management of type 2 diabetes mellitus requires a large armamentarium of drugs acting on the various physiological mechanisms leading to hyperglycemia. Incretin-based therapies have developed as one of the novel pharmacologic therapies in diabetes management. The dipeptidyl peptidase-4 inhibitors (DPP4i) have been recommended as either as monotherapy or as an add-on to metformin because of their proven efficacy, weight-neutrality, low risk of hypoglycemia, and excellent tolerability.[1] [2] Although they may have certain common benefits as a class, the various DPP-4 inhibitors vary considerably in terms of pharmacologic properties and safety profiles.

Gemigliptin was developed by LG Life Sciences in South Korea) and was approved by the South Korea Ministry of Food and Drug safety in June 2012 for the treatment of T2DM.[3] LG Chem also signed licensing agreement with multinational pharmaceutical companies including Sanofi (Paris, France), at present gemigliptin is approved in India, Columbia, Costa Rica, Panama, Ecuador, Thailand and Philippines.

Zemiglo is the brand name of Gemigliptin, which has a novel structure with pyrimidine-piperidine derivatives. Gemigliptin binds to the S1, S2, and S2 extensive subsites of the DPP-4 enzyme. The piperidinone group of gemigliptin binds to the S1 subsite, where the upside F atom on the piperidine ring forms a hydrogen bond with the side chain of Tyr631 and the downside F atom makes a hydrophobic interaction with the side chain of Tyr666 and Tyr662. The key interaction occurs between the CF3 groups on the pyrimidine-piperidine and the S2 extensive subsite of the DPP-4 substrate, which enhances the potency of the drug and increases its selectivity as well.

Gemigliptin is a potent, highly selective, competitive, and long-acting DPP-4 inhibitor. Studies have shown that Gemigliptin is an optimized DPP-4 inhibitor in terms of efficacy, safety and patient compliance for treatment of T2DM. The pharmacokinetics of Gemigliptin has been extensively characterized in healthy subjects and in patients with T2DM. Pharmacokinetic studies have shown that Gemigliptin does not accumulate with multiple dosing and can be administered with or without food.

The elimination of drugs from the body involves the process of metabolism and excretion, and the main routes of excretion are generally via urine and feces. Gemigliptin's elimination route is relatively balanced, while other marketed DPP-4 inhibitors are highly dependent on one or both elimination pathways[4].

---

[1] Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists And American College Of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2016 executive summary. Endocr Pract. 2016;22:84–113.
[2] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care. 2012;35:1364–79.
[3] Kim SH, Lee SH, Yim HJ. Gemigliptin, a novel dipeptidyl peptidase 4 inhibitor: First new anti-diabetic drug in the history of Korean pharmaceutical industry. Arch Pharm Res. 2013;36:1185–8.
[4] Filippatos TD, Athyros VG, Elisaf MS. The pharmacokinetic considerations and adverse effects of DPP-4 inhibitors [corrected]. Expert Opin Drug Metab Toxicol. 2014; 10:787–812.

The efficacy and safety of Gemigliptin was directly compared with other DPP-4 inhibitors in different multicenter, randomized, active-controlled studies. Gemigliptin was compared to Sitagliptin in patients with T2DM inadequately controlled on Metformin. After 24 weeks, the said trial showed that those patients randomized to Gemigliptin have statistically better DPP4-inhibition rate vs Sitagliptin (94.4% vs 91.9%, $p<0.0001$), consequently, with higher proportion of active GLP-1 levels to those randomized to Gemigliptin.[5]

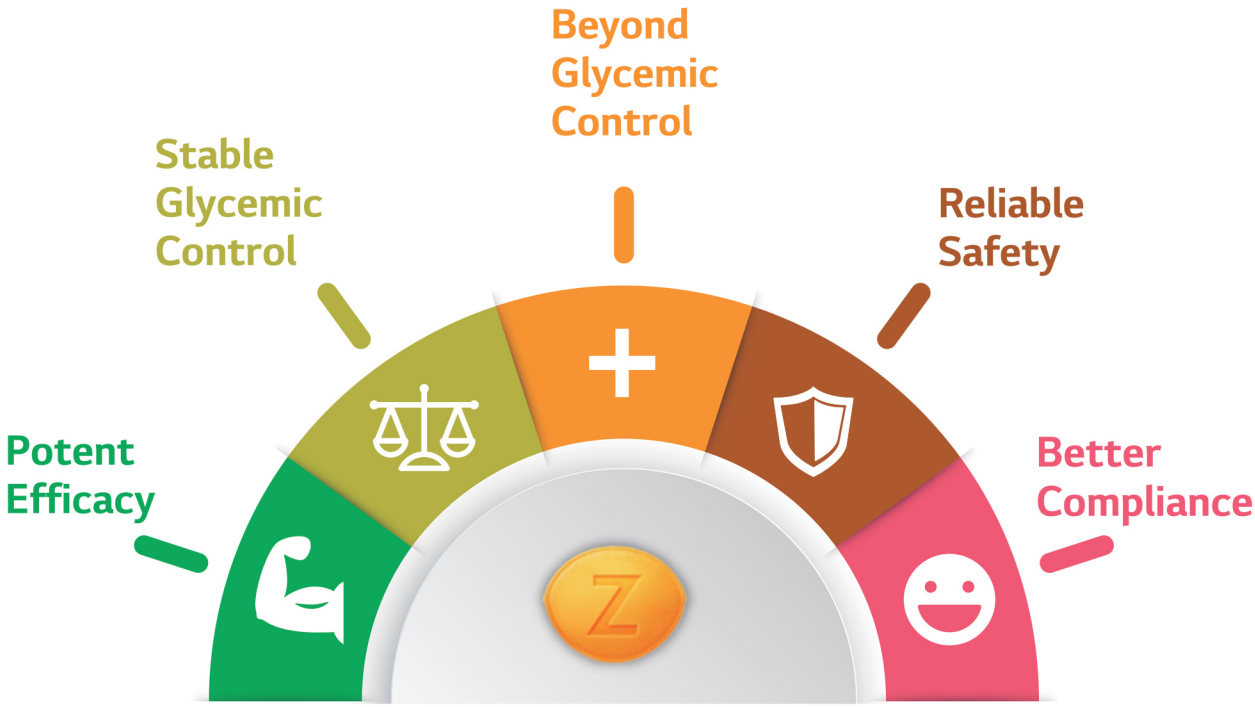
Among patients with Type 2 DM and moderate to severe renal insufficiency, Gemigliptin was found to be significantly better that placebo in terms of lowering mean HBA1c from baseline - 0.82% ± 0.14% (-8.9 ± 1.5 mmol/mol), whereas for placebo, it was 0.38% ± 0.14% (4.2 ± 1.5 mmol/mol), $p<0.001$) at the end of 12 weeks. A 40-week extension study of the GUARD study revealed that Gemigliptin is at par with Linagliptin in in terms of glucose-lowering efficacy, safety and benefits of reducing microalbuminuria among Type 2 Diabetes Mellitus patients with moderate to severe renal impairment.[6]

In terms of MAGE reflecting major glucose fluctuations, DPP-4 inhibitors including Gemigliptin and Sitagliptin were associated with significant improvement compared with Glimepiride at the end of week 12. When considering the total standard deviation of blood glucose levels, glucose variability was more significantly reduced by Gemigliptin compared with Sitagliptin and Glimepiride.[7]

Several clinical studies on Gemigliptin are ongoing and will definitely provide additional evidences of the potential benefits of Gemigliptin in the management of Type 2 Diabetes Mellitus.

[5] Rhee EJ et al., 2012 ADA Poster presentation, 1128-P. Kim SH et al., Diabetes Metab J. 2016;40(5):339–353.
[6] Diabetes Obes Metab. 2017;19(4):590-598. Diabetes Obes Metab. 2018;20(2):292-300.
[7] Diabetes Obes Metab. 2017;19(6):892-896.

LG Chem



Zemiglo® tab. 50 mg

■ **Indication and Usage** Zemiglo® 50 mg is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Zemiglo® can be administered - As monotherapy or - In combination with 1) metformin as initial therapy in treatment naïve patients inadequately controlled by diet and exercise alone 2) metformin in patients with inadequate glycemic control with the maximal tolerated dose of metformin alone 3) metformin and sulfonylurea in patients with inadequate glycemic control with the maximal tolerated dose of metformin and sulfonylurea dual therapy. 4) insulin therapy (insulin monotherapy or with metformin) in patients with inadequate glycaemic control.

■ **Dosage and Administration** The maximum daily recommended dose of Zemiglo® is 50 mg once daily. Zemiglo® can be taken without regard to food. When used in combination with a sulfonylurea or insulin, a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia. No dosage adjustment is required for patients with impaired renal function. No dosage adjustment is required for patients with mild to moderate hepatic impairment function.

■ **Warning and Precautions for Use** [Contraindication] Zemiglo® is contraindicated in patients with 1) a history of serious hypersensitivity reactions, i.e., angioedema or anaphylaxis, to another dipeptidyl peptidase-4 (DPP-4) inhibitor or 2) type 1 diabetes or diabetic ketoacidosis. [Precautions] Zemiglo® is used carefully in patients with 1) taking sulfonylurea 2) cardiac Impairment 3) hepatic impairment 4) acute pancreatitis 5) hypersensitive reaction.

■ **Adverse Reactions** Most common adverse reactions reported ≥ 3% of patients treated with Zemiglo® once daily in monotherapy studies are arthralgia, nasopharyngitis, and bacteriuria. Most common adverse reactions reported in ≥ 3% of patients treated with Zemiglo® once daily in add-on combination study are upper respiratory tract infection, nasopharyngitis, blood amylase increased, lipase increased, and pyrexia.

※ **For more information, please refer to recently updated full prescribing information, including WARNINGS and MEDICATION GUIDE. As approved indications differ by country, consult the local prescribing information available with the manufacture before prescribing this medication.**

The Optimized

Gemigliptin

Zemiglo®

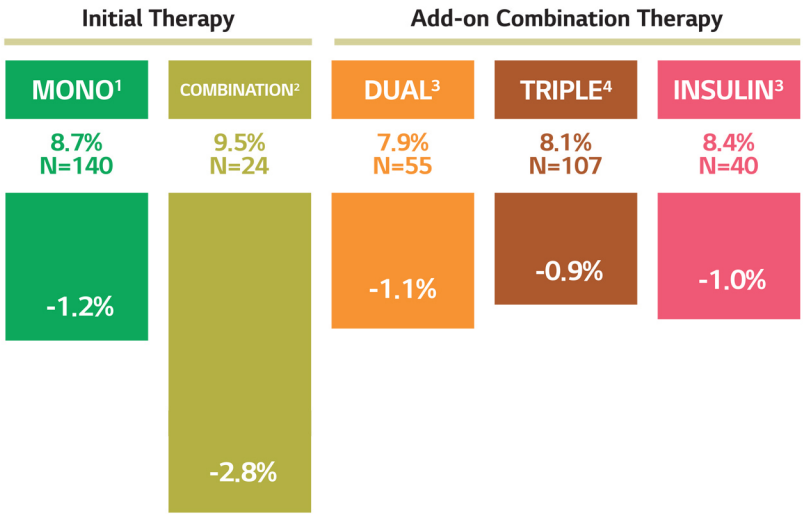
GX INTERNATIONAL

A Filipino Pharmaceutical Company

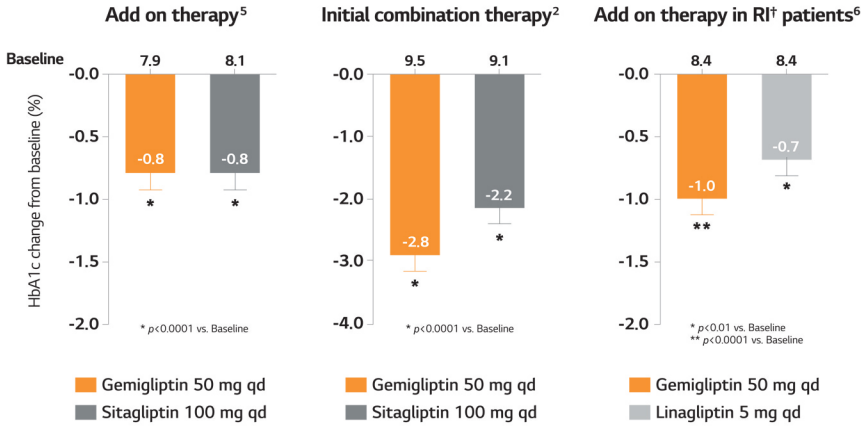
LG Chem

Potent Efficacy

HbA1c Lowering Effects of Gemigliptin*



Head to Head Comparisons of DDP-4 Inhibitors



The Optimized

Gemigliptin

Zemiglo®

*Change in HbA1c from baseline; †Renal Impairment.

References **1.** Diabetes Obes Metab. 2017;19(1):87-97. **2.** Diabetes Obes Metab. 2017;19(6):892-896. **3.** Diabetes Metab J. 2016;40(5):339-353. **4.** Diabetes Obes Metab. 2017;19(5):635-643. **5.** Diabetes Obes Metab. 2013;15(6):523-530. **6.** Diabetes Obes Metab. 2017 Jul 18. doi: 10.1111/dom.13059.

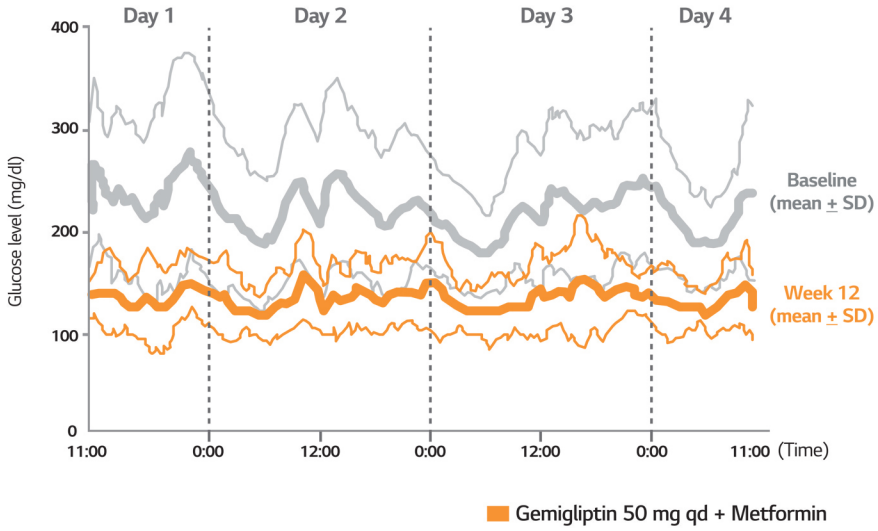
GX INTERNATIONAL

A Filipino Pharmaceutical Company

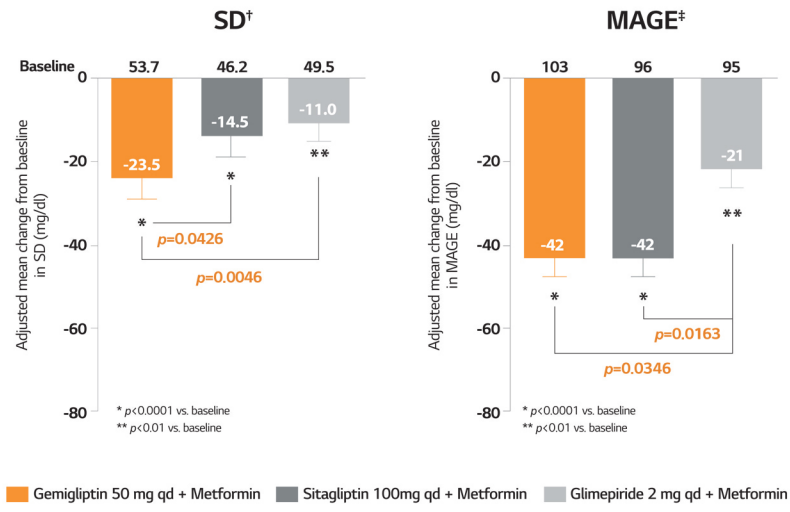
LG Chem

Stable Glycemic Control

Continuous Glucose Profiles with Gemigliptin[1]



Effect of Gemigliptin on Glycemic Variability[1]



The Optimized

Gemigliptin

Zemiglo®

SD†, Standard Deviation of blood glucose levels; MAGE‡: Mean Amplitude of Glycemic Excursion.

References 1. Diabetes Obes Metab. 2017;19(6):892-896.

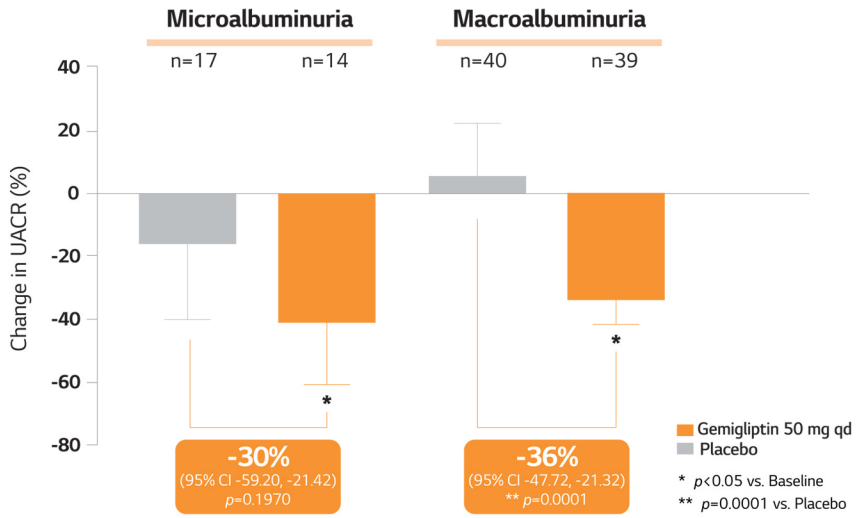
GX INTERNATIONAL

A Filipino Pharmaceutical Company

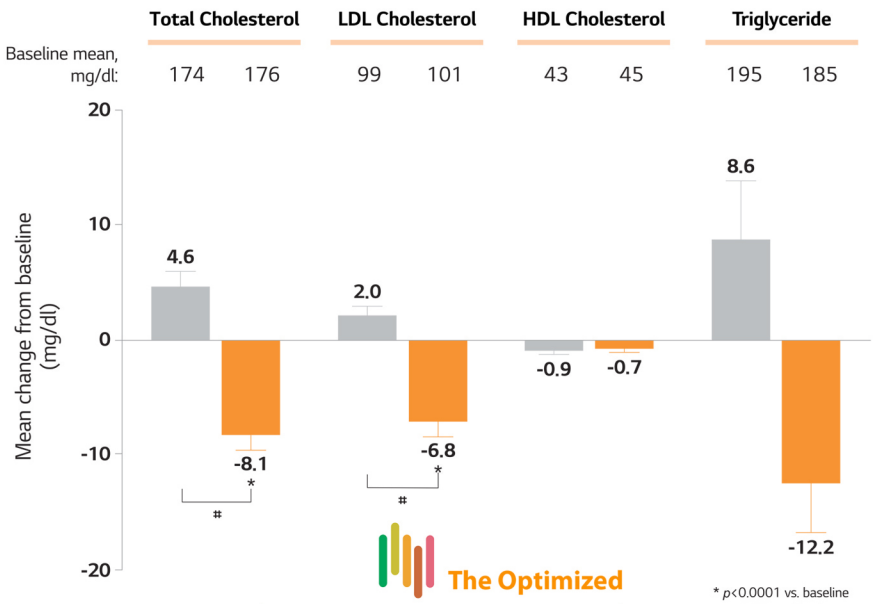
LG Chem

Beyond Glycemic Control

Effect of Gemigliptin on Albuminuria[1]



Effect of Gemigliptin on Lipid profile[1]



The Optimized

Gemigliptin

Zemiglo®

UACR, Urine Albumin-to-Creatinine Ratio.

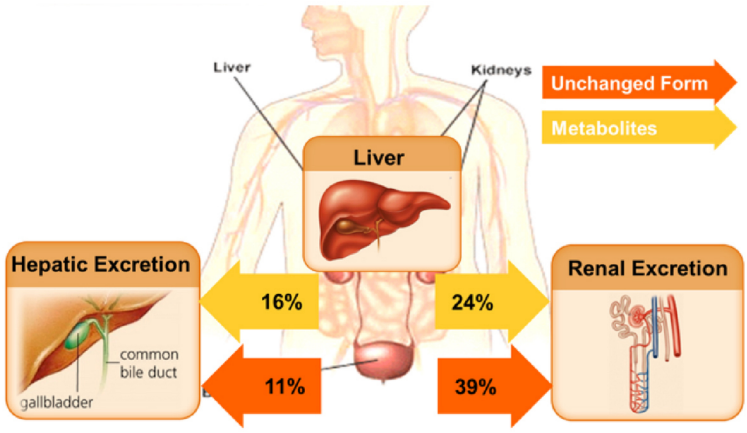
References 1. Diabetes Obes Metab. 2017;19(4):590-598.

GX INTERNATIONAL
A Filipino Pharmaceutical Company

LG Chem

Reliable Safety

Gemigliptin's Balanced Elimination



No dose Adjustment in Renal Impairment [1,3]

Recommended dose of DPP-4 inhibitors in renal impairment

STAGE	Mild RI	Moderate RI	Severe RI
Estimated GFR (mL/min)	≥ 50 to < 80	≥ 30 to < 50	< 30
DPP-4 Inhibitors			
Sitagliptin	100 mg q.d.	50 mg q.d.	25 mg q.d.
Vildagliptin	50 mg b.i.d.	50 mg q.d.	
Linagliptin	5 mg q.d.		
Saxagliptin	5 mg q.d.	2.5 mg q.d.	
Gemigliptin	**50 mg q.d.**		
Alogliptin	25 mg q.d.	12.5 mg q.d.	6.25 mg q.d.

The Optimized
Gemigliptin
Zemiglo®

b.i.d., Twice daily; GFR, Glomerular Filtration Rate; o.d., Once Daily; RI, Renal Impairment.
Adapted from Diabetes Ther. 2015;6:1–5. Diabetes Metab J. 2016;40(5):339–353.

GX INTERNATIONAL
A Filipino Pharmaceutical Company

LG Chem

Better Compliance

Z x 1

Zemiglo®
Once Daily with Single Dose

Renal Impairment [1]					Hepatic Impairment [2]	
ESRD	Severe	Moderate	Mild	Normal	Mild	Moderate
eGFR (ml/min/1.73m²) <15 or dialysis	eGFR (ml/min/1.73m²) 15-29	eGFR (ml/min/1.73m²) 30-59	eGFR (ml/min/1.73m²) 60-89		Child-Pugh A	Child-Pugh B

No Dose Adjustment

ESRD, End-stage Renal Disease; eGFR, estimated Glomerular Filtration Rate.

References 1. Diabetes Obes Metab. 2014;16(10):1028-1031. **2.** Diabetes Metab J. 2016;40(5):339-353.

*The Child-Pugh classfication is based on 2 clinical features (encephalopathy and ascites) and 3 laboratory-based parameters (albumin, bilirubin, and prothrombin time). The Child-Pugh score is the sum of scores of the 5 factors. A sum of 5-6 corresponds to mild (Child Pugh A) hepatic impairment, 7-9 to moderate (Child Pugh B), and 10-15 to severe (Child Pugh C) hepatic impairment.

ESRD, End-stage Renal Disease; eGFR, estimated Glomerular Filtration Rate.

References 1. Diabetes Obes Metab. 2014;16(10):1028-1031. 2. Diabetes Metab J. 2016;40(5):339-353.

The Optimized
Gemigliptin
Zemiglo®

GX INTERNATIONAL
A Filipino Pharmaceutical Company