

**For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory**

**This package insert is continually updated: Please read carefully before using a new pack.**

## **Gemigliptin Tartrate Sesquihydrate Tablets 50mg**

### **Zemiglo<sup>®</sup> 50 mg**

#### **Composition**

Each film coated tablet contains:

Gemigliptin Tartrate sesquihydrate  
(eq. to gemigliptin 50mg).....68.9mg

Excipients .....q.s.

Colours: Titanium dioxide I.P., Sunset yellow FCF Aluminium lake, Red Iron Oxide

#### **Pharmaceutical Form**

Zemiglo is a lemon type, orange colored, film-coated tablet, debossed with LG symbol and a wave pattern on one side and a parting line on the other.

#### **Therapeutic indication**

Zemiglo 50mg 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 50mg can be administered:

1. As monotherapy or
2. In combination with metformin in patients with inadequate glycemic control on metformin alone

#### **Posology and method of administration**

##### Posology

##### *Adults*

The maximum daily recommended dose of Zemiglo is 50 mg once daily. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

##### Additional information on special populations

##### *Renal impairment*

Zemiglo should be used with caution in patient with moderate to severe renal impairment (see section **Warnings and Precautions** and **Pharmacokinetic properties**).

Zemiglo can be administered regardless of the timing of hemodialysis (see section **Warnings and Precautions** and **Pharmacokinetic properties**).

##### *Cardiac Impairment*

There is limited clinical experience in patients with New York Heart Association

(NYHA) Class I cardiac status. Therefore, gemigliptin should be used with caution in this population. Zemiglo is not recommended in patients with NYHA Class II~IV cardiac status.

#### *Hepatic Impairment*

The influence of hepatic impairment on the pharmacokinetics of gemigliptin has not been evaluated. Cautions should be exercised during the use of Zemiglo in this population.

#### *Elderly*

Controlled clinical studies of gemigliptin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients.

#### *Pediatric Population*

Safety and effectiveness in children and adolescents less than 18 years of age have not been established.

#### Method of Administration

Zemiglo can be taken with or without food.

#### **Contraindications**

Zemiglo is contraindicated in patients with

- A history of serious hypersensitivity reactions, i.e., angioedema or anaphylaxis, to another dipeptidyl peptidase-4 (DPP4) inhibitor (see section **Adverse reaction**)
- Type 1 diabetes or diabetic ketoacidosis

#### **Warnings and Precautions**

##### Renal Impairment

Zemiglo should be used with caution in patient with moderate to severe renal impairment (see section **Posology and method of Administration** and **Pharmacokinetic properties**).

Zemiglo can be administered regardless of the timing of hemodialysis (see section **Posology and method of administration** and **Pharmacokinetic properties**).

##### Cardiac Impairment

There is limited clinical experience in patients with New York Heart Association (NYHA) Class I cardiac status. Therefore, gemigliptin should be used with caution in this population. Zemiglo is not recommended in patients with NYHA Class II~IV cardiac status.

##### Hepatic Impairment

The influence of hepatic impairment on the pharmacokinetics of gemigliptin has not been evaluated. Cautions should be exercised during the use of Zemiglo in this

population.

#### Hypersensitive Reaction

Care should be taken when administering in patients with allergic and hypersensitive reactions to any of the ingredients in Zemiglo (see section Adverse Reactions).

#### Acute pancreatitis

In the clinical trials conducted with gemigliptin, no adverse reactions of acute pancreatitis have been reported.

There have been reports of acute pancreatitis in patients taking other dipeptidyl peptidase (DPP-4) receptor inhibitors.

Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain.

If pancreatitis is suspected, gemigliptin should be discontinued; if acute pancreatitis is confirmed, gemigliptin should not be restarted.

Caution should be exercised in patients with a history of pancreatitis.

#### Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking other DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

#### **Interactions**

The responsible enzyme for the metabolism of gemigliptin is CYP3A4. In vitro studies indicated that gemigliptin is not an inhibitor of CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4 and is not an inducer of CYP1A2, 2C8, 2C9, 2C19, or 3A4. Therefore, gemigliptin is unlikely to cause interactions with other drugs that utilize these metabolic pathways. In vitro studies further indicated that gemigliptin did not induce p-glycoprotein (p-gp) while mildly inhibited p-gp mediated transport at high concentration. Therefore, gemigliptin is unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

#### Effects of gemigliptin on other medicinal products

In clinical studies, gemigliptin did not meaningfully alter the pharmacokinetics of metformin and pioglitazone, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cation transporter (OCT).

*Metformin*: Repeated co-administration of 50 mg gemigliptin with 2000 mg metformin, a substrate of OCT1 and OCT2, decreased the  $C_{max}$  of metformin by 13% but did not affect the AUC of metformin.

*Pioglitazone*: Repeated co-administration of 50 mg gemigliptin with 30 mg pioglitazone decreased the AUC and  $C_{max}$  of pioglitazone by 5% and 17%, respectively. However, those of the active metabolites of pioglitazone were not changed.

#### Effects of other medical products on gemigliptin

In clinical studies, metformin and pioglitazone did not meaningfully alter the pharmacokinetics of gemigliptin. Ketoconazole did not meaningfully alter the pharmacokinetics of gemigliptin. Therefore, strong and moderate CYP3A4 inhibitors would not cause clinically meaningful drug interactions. Rifampicin (rifampin), on the other hand, significantly decreased exposure of gemigliptin. Therefore, co-administration with other strong CYP3A4 inducers, including rifampicin (rifampin), dexamethasone, phenytoin, carbamazepine, rifabutin and phenobarbital, is not recommended.

*Metformin*: Repeated co-administration of 50 mg gemigliptin with 2000 mg metformin, a substrate of OCT1 and OCT2, did not meaningfully alter the pharmacokinetics of gemigliptin.

*Pioglitazone*: Repeated co-administration of 50 mg gemigliptin with 30 mg of pioglitazone, a substrate of CYP2C8 and 3A4, did not meaningfully alter the pharmacokinetics of gemigliptin.

*Ketoconazole*: Repeated administration of ketoconazole, a strong inhibitor of CYP3A4, increased the AUC of active moiety, the sum of gemigliptin and its active metabolite, by 1.9-fold.

*Rifampicin*: Repeated administration of rifampicin, a strong inducer of CYP3A4, decreased the AUC and  $C_{max}$  of gemigliptin by 80% and 59%, respectively. The  $C_{max}$  of active metabolite of gemigliptin was not significantly affected while the AUC was decreased by 41%.

#### **Pregnancy**

There are no adequate and well-controlled studies in pregnant women with gemigliptin; therefore, use of gemigliptin is not recommended during pregnancy.

#### **Lactation**

There is no information on excretion of gemigliptin into human milk. Animal studies have shown excretion of gemigliptin in breast milk. Zemiglo should not be used during breast-feeding.

#### **Effects on ability to drive and use machines**

Zemiglo has no known influence on the ability to drive and use machines.

## **Adverse reaction**

### Summary of the safety profile

There were 748 patients with type 2 diabetes, including 480 patients treated with gemigliptin, randomized in three double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of gemigliptin on glyceemic control.

The overall incidence of adverse events in patients treated with gemigliptin was similar to placebo and active-control group.

Discontinuation of therapy due to adverse events was similar in patients who received gemigliptin as compared to placebo (0.79% as compared to 0.78%).

Across all the clinical studies, there was no serious adverse event (SAE) related to gemigliptin.

### Tabulated list of adverse reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reactions are listed by SOC (system organ class) and frequency. Frequencies are defined as Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1,000$ ), not known (cannot be estimated from the available data)

Two placebo-controlled monotherapy studies, one of 12- and one of 24-week duration, included patients treated with gemigliptin 50 mg once daily.

Table 1 summarizes the adverse reactions reported in  $\geq 1\%$  of patients treated with gemigliptin 50mg once daily.

**Table 1.** Frequency of adverse reactions by system organ class treated with gemigliptin 50 mg once daily in two placebo-controlled monotherapy studies

<b>System Organ Class</b>	<b>Gemigliptin 50mg qd</b>
Adverse Reaction	<b>N=126(%)</b>
<b>Metabolism and nutrition disorders</b>	
Hypoglycaemia	Common

One active-controlled add-on combination therapy study with metformin included patients treated with gemigliptin 25 mg twice daily, gemigliptin 50 mg once daily and sitagliptin 100 mg once daily.

Table 2 summarizes the adverse reactions reported in  $\geq 1\%$  of patients treated with gemigliptin 25mg twice daily, gemigliptin 50mg once daily.

**Table 2.** Frequency of adverse reactions by system organ class treated with gemigliptin 50 mg once daily in one active-controlled add-on combination study)

<b>System Organ Class</b> Adverse Reaction	<b>Gemigliptin</b> <b>50mg qd</b> N=140(%)	<b>Gemigliptin</b> <b>25mg bid</b> N=141(%)
<b>Infections and infestations</b>		
Asymptomatic bacteriuria	Uncommon	Common
<b>Investigations</b>		
Blood amylase increased	Common	-
Lipase increased	Common	Common
<b>Skin and subcutaneous tissue disorders</b>		
Urticaria	-	Common

#### Description of selected adverse reactions

##### Hypoglycemia

In two placebo-controlled studies of gemigliptin 50 mg once daily as monotherapy, 2 patients (1.59%) reported hypoglycemia. In the active controlled study of gemigliptin 50 mg once daily as add-on combination therapy, 1 patient(0.71%) reported hypoglycemia during the first 24-weeks and 2 patients (1.8%) reported hypoglycemia during the latter 28-weeks. The hypoglycemia experienced by patients in clinical trials was considered to be of mild in intensity and patients fully recovered.

##### Anaphylactic reactions

In the active-controlled add-on combination study, two patients(1.71%) receiving 25 mg gemigliptin twice daily on a stable dose of metformin in the first 24-weeks and 50 mg once daily in the latter 28 weeks reported anaphylactic reactions, which was not related to gemigliptin exposure (see section **Contraindications** and **Warnings and Precautions**).

##### **Overdose**

During clinical trials in healthy subjects, doses of up to 600 mg gemigliptin were repeatedly administered for duration of 10 days. One case of increased heartbeat was observed at a dose of 600 mg gemigliptin,. There is no experience with daily doses above 600 mg in clinical studies. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as indicated by the patient's clinical status.

## **Pharmacodynamic properties**

Pharmacotherapeutic group: Medicines used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH06(not determined).

### Mechanism of Action

Zemiglo is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which enhances the level of active incretin hormones, including GLP-1 and GIP, thereby reducing blood glucose levels. Active GLP-1 and GIP promote insulin production and release from pancreatic beta cells. GLP-1 also lowers the secretion of glucagon from pancreatic alpha cells, thereby resulting in a decreased hepatic glucose production. However these incretins are rapidly degraded by the DPP-4. Gemigliptin selectively inhibits DPP-4 activity, enhancing prolonged activation of incretin hormones. Gemigliptin demonstrates > 3,400-fold and > 9,500-fold selectivity versus DPP-8 and DPP-9, respectively.

### Clinical Efficacy and Safety

The benefit of administering gemigliptin in patients with T2DM and the risk associated with this treatment has been evaluated in the clinical program conducted in total 700 subjects enrolled in 3 clinical trials.

The efficacy and safety of gemigliptin monotherapy was evaluated in a placebo-controlled Phase II study of 12 week duration. The mean change in HbA1c from baseline at Week 12 was -0.98%, -0.74% and -0.78% (when adjusted with placebo data, -0.92%, -0.68% and -0.72%) at dosage levels of 50mg, 100mg and 200mg, respectively.

The efficacy and safety of gemigliptin monotherapy was evaluated in a placebo-controlled Phase III study of 24 week duration. The analysis of covariance for HbA1c change from baseline at Week 24 (W24 - W0) demonstrated that placebo-subtracted mean HbA1c reduction from baseline was -0.705% [90% CI -1.041 to -0.368]. Therefore, the clinical efficacy of gemigliptin was demonstrated to be superior to that of the placebo group. The study was extended through Week 52. In the extended part of the study, an analysis of HbA1c change from baseline revealed consistent glycemic control effect of gemigliptin over a period of 52 weeks. Further decrease in HbA1c was observed with continued treatment of gemigliptin 50 mg in the latter 28 weeks and the degree of change from baseline at Week 52 (-0.87%) was still clinically and statistically significant ( $p < .0001$ ).

The efficacy and safety of gemigliptin add-on combination therapy was evaluated in a active-controlled Phase III study of 24 week duration. The analysis of covariance for HbA1c change from baseline at Week 24 (W24 - W0) demonstrated that the between-group difference (each regimen group of Gemigliptin-Sitagliptin group) in the least square mean change from baseline was 0.056% [90% CI -0.117 to 0.23] for 50 mg, qd group and 0.04% [90% CI -0.121 to 0.2] for 25 mg, bid group. Therefore, the clinical efficacy of gemigliptin was demonstrated to be at least comparable with that of the comparator, sitagliptin. The study was extended through Week 52. In the extended part of the study, the change in HbA1c from baseline was clinically and statistically

significant ( $p < .0001$ ) throughout the duration of 52 weeks in all treatment groups. The decrease in HbA1c was most prominent at Week 6 followed by further gradual decrease thereafter. Decreased HbA1c level was well maintained in all three groups during the extended 28 weeks.

The data collected in clinical studies demonstrated that gemigliptin was well tolerated and displayed an overall safety profile that is at least comparable with that of the comparator.

## **Pharmacokinetic properties**

### Absorption

Following a single oral administration of gemigliptin to healthy subjects, gemigliptin was rapidly absorbed, with  $T_{max}$  occurring 1 to 5 hours post-dose. At the recommended dose of 50 mg,  $C_{max}$  and AUC were 62.7 ng/mL and 743.1 ng•hr/mL, respectively. The system exposure was increased in a dose-proportional manner in the range of 25 ~ 400 mg.

### Distribution

*In vitro* plasma protein binding is 29% for gemigliptin and 35% ~ 48 % for the metabolites.

### Biotransformation

The responsible enzyme for the metabolism of gemigliptin is CYP3A4. In plasma, gemigliptin and the major metabolite (LC15-0636) accounted for 65% ~ 100% and 0% ~ 17.5% of the sample radioactivity. LC15-0636, an hydroxylated metabolite of gemigliptin, is pharmacologically active and two times more potent than gemigliptin. *In vitro* studies indicated that gemigliptin is not an inhibitor of CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4 and is not an inducer CYP1A2, 2C8, 2C9, 2C19, or 3A4. Therefore, gemigliptin is considered unlikely to cause interactions with other drugs that utilize these metabolic pathways.

### Elimination

Following oral administration of [ $^{14}$ C]gemigliptin to healthy subjects, the administered radioactivity was recovered in feces (27%) or urine (63%). The elimination half-life after oral administration is approximately 17 hr and 24 hr for gemigliptin and LC15-0636, respectively.

### Renal Impairment

The influence of renal impairment on the pharmacokinetics of gemigliptin has been evaluated. In patients with mild (CrCl: 50 ~ 80 mL/min), moderate (CrCl: 30 ~ 50 mL/min), severe (CrCl: <30 mL/min) and end stage renal disease (on hemodialysis),  $AUC_{inf}$  increased 1.20-, 2.04-, 1.50- and 1.69-fold for gemigliptin and 0.91-, 2.17-, 3.07- and 2.66-fold for LC15-0636, when compared with the normal kidney function group. Overall active moiety, the sum of gemigliptin and LC15-0636, was increased less than or approximately 2-fold in patients with moderate and severe renal impairment.

In patients with moderate or severe renal impairment, the plasma level of gemigliptin is

increased compared to subjects with normal renal function. Therefore, gemigliptin should be used with caution in patients with moderate to severe renal impairment (see section **Posology and method of administration** and **Warnings and Precautions**).

In patients requiring haemodialysis, gemigliptin can be administered regardless of the timing of haemodialysis (see section **Posology and method of administration** and **Warnings and Precautions**).

#### Gender

No dose adjustment is necessary based on gender. The differences in  $C_{max}$  and  $AUC_{inf}$  were not clinically significant.

#### Race

Caucasian subjects demonstrated 28% decrease in  $C_{max}$  and 20% increase in AUC when compared with Korean subjects.

#### Geriatric

Of the total number of subjects (N=754) in premarketing Phase II and III clinical studies of gemigliptin, 88 patients (11.7%) were 65 years and over. Controlled clinical studies of gemigliptin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients. Zemiglo should be used with caution in elderly patient because physiological functions including liver and kidney are usually decreased in this population.

#### **Shelf life**

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#### **Manufactured by:**

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#### **Updated : June 2017**

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