1. NAME OF THE MEDICINAL PRODUCT
Zemiglo 50 mg Film-Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains gemigliptin tartrate sesquihydrate, equivalent to 50 mg gemigliptin.
For a full list of excipients, see section 6.1.

3. 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.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
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 50 mg can be administered
1. As monotherapy or
2. In combination with
• metformin as initial therapy in treatment naïve patients with inadequate glycemic control by diet and exercise.
• metformin in patients with inadequate glycemic control with maximal tolerated dose of metformin alone.
• metformin and sulfonylurea in patients with inadequate glycemic control with the maximal tolerated dose of metformin and sulfonylurea dual therapy.
• insulin (with or without metformin) in patients with inadequate glycemic control with insulin alone or insulin and metformin dual therapy.
• dapagliflozin and metformin in patients with inadequate glycemic control with dapagliflozin and metformin dual therapy.

4.2 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.

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 (see section 4.4).

Additional information on special populations
Renal impairment
For patients with renal impairment, no dose adjustment is required (see section 5.1 and 5.2).

Hepatic Impairment
No dose adjustment is necessary for patients with mild or moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment. Therefore, caution should be exercised in this population (see section 5.2).

Elderly
The efficacy and safety of gemigliptin were not different between young and elderly patients. However, Zemiglo should be used with caution in elderly patient because physiological functions including liver and kidney are usually decreased in this population (see section 5.1).

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.

4.3 Contraindications
Zemiglo is contraindicated in patients with
• A history of serious hypersensitivity reactions, i.e., angioedema or anaphylaxis, to another dipeptidyl peptidase-4 (DPP-4)

inhibitor (see section 4.8).
• Type 1 diabetes or diabetic ketoacidosis.

4.4 Special warnings and precautions for use
Renal Impairment
No adjustment is required (see section 5.1 and 5.2).

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
No dose adjustment is necessary for patients with mild or moderate hepatic impairment. There is no clinical experience in patients with severe hepatic impairment. Therefore, caution should be exercised 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 4.8).
Post-marketing reports of severe hypersensitivity reactions in patients treated with Zemiglo have been reported. These reactions include Stevens-Johnson syndrome. If a severe hypersensitivity reaction is suspected, Zemiglo should be discontinued. Other potential causes for the reaction should be assessed, and alternative treatment for diabetes should be initiated.

Acute Pancreatitis
Pancreatitis has been reported in patients taking Zemiglo. Therefore, patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, gemigliptin should be discontinued and should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Use with Medicinal Products Known to Cause Hypoglycemia
Sulfonylurea or insulin is known to cause hypoglycemia. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia when used in combination with Zemiglo.

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.

Excipient warnings
Gemigliptin tablet contains sunset yellow FCF which may cause allergic reactions.

Bullous pemphigoid
There have been post-marketing reports of bullous pemphigoid requiring hospitalization in patients taking other DPP-4 inhibitors. In reported cases, patients generally recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Patients should be instructed to report development of blisters or erosions to their doctors while receiving Zemiglo. If bullous pemphigoid is suspected, Zemiglo should be discontinued and a dermatologist should be consulted for diagnosis and proper treatment.

4.5 Interaction with other medicinal products and other forms of interaction
In vitro assessment of interactions
The responsible enzyme for the metabolism of gemigliptin is CYP3A4. *In vitro* studies indicated that gemigliptin and its active metabolite are not an inhibitor of CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4 and are 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.

In vivo assessment of interactions
Effects of gemigliptin on other medicinal products
In clinical studies, gemigliptin did not meaningfully alter the pharmacokinetics of metformin, pioglitazone, glimepiride, rosuvastatin, dapagliflozin, and empagliflozin providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP2C8, CYP2C9, CYP3A4, organic cation transporter (OCT), and UDP-glucuronosyltransferase (UGT).

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 at steady state.

Pioglitazone: Repeated co-administration of 200 mg gemigliptin with 30 mg pioglitazone, a substrate of CYP2C8 and 3A4, decreased the AUC and C_{max} of pioglitazone by 15% and 17%, respectively. However, those of the active metabolites of pioglitazone were not changed at steady state.

Glimepiride: Co-administration of multiple doses of 50 mg gemigliptin with a single dose of 4 mg glimepiride, a substrate of CYP2C9, did not meaningfully alter the pharmacokinetics of glimepiride at steady state.

Rosuvastatin: Repeated co-administration of 50 mg gemigliptin with 20 mg rosuvastatin, a substrate of CYP2C9 and 3A4, did not meaningfully alter the pharmacokinetics of rosuvastatin at steady state.

Dapagliflozin: Repeated co-administration of 50 mg gemigliptin with 10 mg of dapagliflozin, substrate of UGT1A9, did not meaningfully alter the pharmacokinetics of dapagliflozin at steady state.

Empagliflozin: Repeated co-administration of 50 mg gemigliptin with 25mg of empagliflozin, substrate of UGT2B7, UGT1A3, UGT1A8, and UGT1A9, did not meaningfully alter the pharmacokinetics of empagliflozin at steady state.

Effects of other medical products on gemigliptin
In clinical studies, metformin, pioglitazone, rosuvastatin, dapagliflozin, and empagliflozin did not meaningfully alter the pharmacokinetics of gemigliptin. Ketoconazole did not meaningfully alter the pharmacokinetics of gemigliptin and its active metabolite. 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 did not meaningfully alter the pharmacokinetics of gemigliptin and its active metabolite at steady state.

Pioglitazone: Repeated co-administration of 200 mg gemigliptin with 30 mg of pioglitazone did not meaningfully alter the pharmacokinetics of gemigliptin and its active metabolite at steady state.

Ketoconazole: Co-administration of multiple doses of 400 mg ketoconazole once daily, a strong inhibitor of CYP3A4, with a single dose of 50 mg gemigliptin increased the AUC of active moiety, the sum of gemigliptin and its active metabolite, by 1.9-fold at steady state.

Rifampicin: Co-administration of multiple doses of 600 mg rifampicin once daily, a strong inducer of CYP3A4, with a single dose of 50 mg gemigliptin, 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 36% at steady state.

Rosuvastatin: Repeated co-administration of 50 mg gemigliptin with 20 mg rosuvastatin did not meaningfully alter the pharmacokinetics of gemigliptin at steady state.

Dapagliflozin: Repeated co-administration of 50 mg gemigliptin with 10 mg of dapagliflozin did not meaningfully alter the pharmacokinetics of gemigliptin at steady state.

Empagliflozin: Repeated co-administration of 50 mg gemigliptin with 25 mg of empagliflozin did not meaningfully alter the pharmacokinetics of gemigliptin at steady state.

4.6 Pregnancy and lactation
Fertility

No studies on the effect on human fertility have been conducted for gemigliptin. Animal studies with gemigliptin do not indicate harmful effects to fertility in male and female rat.

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.

4.7 Effects on ability to drive and use machines
When driving or using machines, caution should be exercised as dizziness has been reported. In addition, patients should be alerted to the risk of hypoglycemia when Zemiglo is used in combination with other antidiabetic medicinal products known to cause hypoglycemia (e.g. sulfonylureas, insulin).

4.8 Undesirable effects
There were 2,281 patients with type 2 diabetes, including 1,351 patients that were randomized into gemigliptin group in 10 controlled clinical safety and efficacy studies conducted to evaluate the effects of gemigliptin on glycemic control.

Safety data were collected from a total of 1,606 patients exposed to gemigliptin at a dose of 50 mg per day in controlled clinical trials of monotherapy or combination therapy of 12 weeks or more. Of these patients, 221 patients received gemigliptin alone and 1,385 received it in combination with other medications.

Serious adverse reactions related to gemigliptin have not been reported in all 10 clinical studies.

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.

Tabulated summary of adverse reactions
Table 1 presents adverse reactions for over 12 weeks which have been reported from the pooled analysis of 10 randomized, controlled clinical studies. The adverse reactions are listed by SOC (system organ class) and PT (Preferred Term) with frequency. Frequencies are defined as Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1,000), or not known (cannot be estimated from the available data).

Table 1. Frequency of adverse reactions for 12 or more by system organ class in patients treated with gemigliptin from the pooled analysis

System Organ Class Adverse Reaction	Number of Patients with Adverse Drug Reactions (percentage)	Frequency
Gastrointestinal disorders		
Dyspepsia	12 (0.7)	Uncommon
Constipation	4 (0.2)	Uncommon
Diarrhea	4 (0.2)	Uncommon
Nausea	4 (0.2)	Uncommon
Abdominal pain upper	3 (0.2)	Uncommon
Gastric disorder	2 (0.1)	Uncommon
Gastrointestinal disorder	2 (0.1)	Uncommon
Eructation	1 (< 0.1)	Rare
Gastritis hemorrhagic	1 (< 0.1)	Rare
Hyperchlorhydria	1 (< 0.1)	Rare
General disorders and administration site conditions		
Swelling	1 (< 0.1)	Rare
Infections and infestations		
Asymptomatic bacteriuria	4 (0.2)	Uncommon
Nasopharyngitis	3 (0.2)	Uncommon
Upper respiratory tract infection	1 (< 0.1)	Rare

Urinary tract infection	1 (< 0.1)	Rare
Investigations		
Lipase increased	10 (0.6)	Uncommon
Amylase increased	3 (0.2)	Uncommon
Blood creatine phosphokinase increased	2 (0.1)	Uncommon
Alanine aminotransferase abnormal	1 (< 0.1)	Rare
Alanine aminotransferase increase	1 (< 0.1)	Rare
Hepatic enzyme increased	1 (< 0.1)	Rare
Pancreatic enzymes increased	1 (< 0.1)	Rare
Weight decreased	1 (< 0.1)	Rare
Weight increased	1 (< 0.1)	Rare
Metabolism and nutrition disorders		
Hypoglycemia	17 (1.1)	Common
Decreased appetite	3 (0.2)	Uncommon
Hyperglycemia	2 (0.1)	Uncommon
Hypoglycemia unawareness	2 (0.1)	Uncommon
Hypertriglyceridemia	1 (< 0.1)	Rare
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (< 0.1)	Rare
Myalgia	1 (< 0.1)	Rare
Nervous system disorders		
Dizziness	2 (0.1)	Uncommon
Headache	2 (0.1)	Uncommon
Diabetic neuropathy	1 (< 0.1)	Rare
Hypoaeesthesia	1 (< 0.1)	Rare
Tension headache	1 (< 0.1)	Rare
Psychiatric disorders		
Insomnia	1 (< 0.1)	Rare
Reproductive system and breast disorders		
Vulvovaginal pruritus	1 (< 0.1)	Rare
Respiratory, thoracic and mediastinal disorders		
Epistaxis	1 (< 0.1)	Rare
Skin and subcutaneous tissue disorders		
Dermatitis	1 (< 0.1)	Rare
Photosensitivity reaction	1 (< 0.1)	Rare
Pruritis	1 (< 0.1)	Rare
Rash	1 (< 0.1)	Rare
Urticaria	1 (< 0.1)	Rare

Post-marketing surveillance

Table 2 presents adverse reactions which have been reported during post-marketing surveillance. The adverse reactions are listed by SOC and PT with frequency. Frequencies are defined as Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1,000), or not known (cannot be estimated from the available data).

Table 2. Frequency of adverse reactions reported from post-marketing surveillance of Zemiglo

System Organ Class Adverse Reaction	**Frequency N=3,036**
Gastrointestinal disorders	
Dyspepsia	Uncommon
Constipation	Rare
Nausea	Rare

Nervous system disorders	
Headache	Rare
Dizziness	Rare
Skin and subcutaneous tissue disorders	
Rash	Rare
Metabolism and nutrition disorders	
Hypoglycemia	Rare
Investigations	
Blood creatinine increased	Rare
Ear and labyrinth disorders	
Motion sickness	Rare

Spontaneous global post-marketing reports
The following adverse reactions have been additionally reported during post-marketing use of the product. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Pneumonia, Vomiting, Edema peripheral, Asthenia, Stevens-Johnson syndrome, Rash pruritic, Pyrexia, Gastritis, Arthralgia, Swelling face, Lip swelling, Pancreatitis

Description of selected adverse reactions
Hypoglycemia
Hypoglycemia was commonly reported in controlled clinical trials of gemigliptin over 12 weeks. In all studies, the majority of reported hypoglycemia was mild and recovered. The incidence of hypoglycemia was similar among treatment groups, including placebo, in all studies. The incidence of hypoglycemia was higher in the sulfonylurea and insulin add-on studies compared to the other studies.

Pancreatitis
Although pancreatitis has not been reported, increased levels of lipase, for which a causal relationship with gemigliptin cannot be ruled out, have been reported, though uncommonly. In the results of controlled clinical trials of monotherapy and combination therapy over 12 weeks with gemigliptin, increased lipase levels were observed in 0.6% of patients, which were mild or moderate, and most recovered.

Hypersensitivity
Hypersensitivity reactions related to gemigliptin have not been reported in all 10 clinical studies.

Bullous pemphigoid
There have been post-marketing reports of bullous pemphigoid requiring hospitalization in patients taking other DPP-4 inhibitors. There have been no reports of bullous pemphigoid in monotherapy and combination therapy controlled clinical trials of gemigliptin of 12 weeks or longer.

4.9 Overdose
During clinical trials in healthy subjects, multiple doses of up to 600 mg gemigliptin were administered for duration of 10 days. One case of increased heartbeat was observed at a single 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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Medicines used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH06.

Mechanism of Action
Zemiglo is a member of a class of oral anti-hyperglycemic 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 glucacon 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-9 and DPP-8, respectively.

Clinical Efficacy and Safety

Over 2,200 patients with type 2 diabetes have been included in randomized, controlled clinical trials. Overall, gemigliptin improved glycemic control when used as monotherapy or in combination treatment.

Gemigliptin dose finding

The efficacy and safety of gemigliptin monotherapy was evaluated in a placebo-controlled Phase II study of 12 weeks 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 50 mg, 100 mg and 200 mg, respectively.

Gemigliptin as monotherapy

The efficacy and safety of gemigliptin monotherapy was evaluated in a placebo-controlled Phase III study of 24 weeks duration. The analysis of covariance (ANCOVA) for HbA1c change from baseline at Week 24 (W24 - W0) showed that placebo-subtracted mean HbA1c change from baseline was -0.705% [95% confidence interval (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<0.0001).

Gemigliptin as add-on to metformin therapy

The efficacy and safety of gemigliptin add-on combination therapy were evaluated in an active-controlled Phase III study of 24 week duration. The ANCOVA for HbA1c change from baseline at Week 24 (W24 - W0) showed that the between–group difference (each regimen group of gemigliptin-sitagliptin group) in the least square (LS) 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<0.0001) 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.

Gemigliptin as add-on to a combination of metformin and sulfonylurea therapy

The efficacy and safety of gemigliptin triple combination therapy with metformin and sulfonylurea were evaluated in a placebo-controlled Phase III study of 24 weeks duration. An ANCOVA was conducted using the HbA1c value at baseline as a covariate and including the glimepiride reduction as a factor in relation to the change in HbA1c at Week 24. In the main population for analysis, the LS mean of the HbA1c change at Week 24 after study treatment was -0.877±0.166% (p<0.0001) in gemigliptin group and -0.012±0.179% (p=0.9476) in the placebo group, showing a significant reduction compared to the baseline in the gemigliptin group. As the 95% CI for the difference in change between the treatment groups was (-1.092%, -0.638%), i.e., its upper limit was less than 0, the superiority of the gemigliptin was demonstrated.

Gemigliptin and metformin as initial therapy

The efficacy and safety of gemigliptin initial combination therapy with metformin were evaluated in an active-controlled Phase III study of 24 weeks duration. For the change of HbA1c from baseline at Week 24, analysis of covariance was performed. As a result, the 95% CI for between group difference in LS means of HbA1c changes in combination therapy group and each monotherapy group were (-1.02%, -0.63%) in combination therapy group compared with gemigliptin group and (-0.82%, -0.41%) in combination therapy group compared with metformin group, respectively. This showed that the upper limits of both CIs were less than zero (p<0.001), confirming superiority of the combination therapy.

Gemigliptin therapy in patients with renal impairment

The efficacy and safety of gemigliptin monotherapy or its combination therapy with insulin and sulfonylurea in type 2 diabetes patients with moderate or severe renal impairment were evaluated in a double-blind study for 52 weeks duration. The change in HbA1c at Week 12 was -0.96% and 0.21% in the gemigliptin and placebo groups, respectively, showing significant difference between the groups (p<0.0001). Adjusted mean difference between the groups was -1.20% with two-sided 95% CI of -1.53% to -0.87%. The upper limit of the 95% CI for the difference in HbA1c change (HbA1c at week 12 – HbA1c at week 0) between groups was lower than 0, which demonstrates the superiority of the gemigliptin over the placebo. The efficacy of gemigliptin was maintained for 52 weeks.

Gemigliptin as add-on to insulin (+/- metformin) therapy
The efficacy and safety of gemigliptin added-on to insulin alone or insulin in combination with metformin in patients with type 2 diabetes were evaluated in a randomized, placebo-controlled, parallel-group, double-blind, phase III study of 24 weeks duration. The primary efficacy endpoint was analysed using an ANCOVA model, with metformin use and country as fixed factors and baseline value as a covariate. In the full analysis set, the LS mean (SE) change from baseline HbA1c after 24 weeks was -0.816% (0.1150%) with gemigliptin and -0.131% (0.1357%) with placebo. The between-group difference was -0.685%, and its 95% CI was (-0.941%, -0.429%). The upper limit of the 95% CI for the between-group difference in HbA1c changes was less than 0, suggesting superior glycemic control of the gemigliptin compared to the placebo.

Gemigliptin as add-on to dapagliflozin and metformin therapy
The efficacy and safety of gemigliptin added-on to dapagliflozin and metformin in patients with type 2 diabetes were evaluated in a multicenter, randomized, placebo-controlled, parallel group, double-blind, phase III study for 24 weeks. After 24 weeks, the average change in HbA1c from baseline was -0.86% and -0.20% in the gemigliptin and placebo groups, respectively. The difference in HbA1c change compared to placebo was -0.66% (95% CI: -0.80, -0.52), which was a statistically significant decrease (*p*-value <0.0001).

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.

Elderly Population
Of the 2,281 patients who participated in the Phase 2, 3, and 4 clinical trials of gemigliptin, 465 (20.4%) were 65 years of age or older. Safety efficacy in older adults was similar to younger patients. Because elderly patients typically have decreased physiologic functions, including liver and kidney function, dosing should be monitored and administered with caution.

5.2 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 50~400 mg.

Distribution
In vitro human plasma protein binding is 29% for gemigliptin and 35%~48 % for the metabolites including major active metabolite.

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, a 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.

Hepatic Impairment
The influence of hepatic impairment on the pharmacokinetics of gemigliptin has been evaluated. In mild and moderate hepatic impairment, exposure to gemigliptin (AUC) after single dosing was 50% and 80% higher than in healthy subjects. Formation of LC15-0636, a metabolite of gemigliptin, was only slightly affected by mild hepatic impairment (5% to 10% lower), while in moderate hepatic impairment, formation of LC15-0636 was about 30% lower compared to healthy subjects. Urinary excretion

parameters were not markedly influenced by hepatic impairment, so the decrease in total clearance of gemigliptin observed in hepatic impairment is due a decreased metabolization rate of gemigliptin. Half-lives of gemigliptin and of LC15-0636 were slightly increased in hepatic impairment.

In mild and moderate hepatic impairment, inhibition of DPP-4 was slightly decreased compared to healthy subjects (5% to 10%), however, neither the effect on AUEC nor on E_{max} of DPP-4 inhibition was statistically significant. It is expected that dose adjustment would not be required in mild and moderate hepatic impairment based on the efficacy and safety profile of gemigliptin in clinical and non-clinical studies.

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 5% decrease in AUC_{inf} when compared with Korean subjects.

5.3 Preclinical safety data
A two-year carcinogenicity study was conducted in male and female rats given oral doses of gemigliptin of 50, 150 and 450 mg/kg/day. No evidence of carcinogenicity with gemigliptin was found in either male or female rats. This dose results in exposures approximately 129~170 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 50 mg/day based on AUC comparisons. A 6-month carcinogenicity study has been performed in TgrasH2 transgenic mice at doses of 200, 400 and 800 mg/kg/day in males and 200, 600 and 1200 mg/kg/day in females. There was no evidence of carcinogenicity with gemigliptin at a dose of 1200 mg/kg/day, approximately 87 times the human exposure at the maximum recommended daily dose.

Genotoxicity assessments in the Ames test, chromosomal aberrations test and *in vivo* micronucleus tests in mice and rats were negative.

The fertility of gemigliptin was not affected at dose of 800 mg/kg/day in rat. Gemigliptin was not teratogenic up to 200 mg/kg/day in rats and 300 mg/kg/day in rabbits, which are respectively 83 and 153 times human exposure at the MRHD of 50 mg/day.

Gemigliptin at dose of 800 mg/kg/day in rat, approximately 264 times human exposure at the MRHD of 50 mg/day, increased the incidence of fetus cleft palate malformation, dilated renal pelvis, misshapen thymus and sternoschisis, with increasing dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core
Microcrystalline Cellulose (Type 102)
Microcrystalline Cellulose (Type 101)
Croscarmellose Sodium
Stearyl Fumarate Sodium
Opadry II 85F43172

Film coating
Polyvinyl Alcohol
Titanium Dioxide
Polyethylene Glycol 3350
Talc
FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake
Red Iron Oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store below 30°C in tight container.

6.5 Nature and contents of container
Clear blisters (PVC/PVDC and aluminum). Pack of 28 film-coated tablets in unit dose blisters.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER
Pharmaniaga Marketing Sdn Bhd (198401005734)
No. 7, Lorong Keluli 1B,
Kawasan Perindustrian Bukit Raja Selatan,
Seksyen 7, 40000 Shah Alam,
Selangor Darul Ehsan, Malaysia.

8. DATE OF REVISION OF THE TEXT
28.08.2025