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Summary of Product Characteristics on March 29, 2022.

Zemimet® SR Tab. 50/1000 mg

1. NAME OF THE MEDICINAL PRODUCT

Zemimet® SR 50/1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Zemimet® SR 50/1000 mg contains gemigliptin tartrate sesquihydrate, equivalent to 50 mg gemigliptin, and 1000 mg of metformin hydrochloride sustained release. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Zemimet® SR 50/1000 mg is oblong shaped, brown colored, film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Zemimet® SR 50/1000 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

4.2 Posology and method of administration

Posology

Adult patients with type 2 diabetes mellitus

Zemimet® SR 50/1000 mg should generally be administered once daily with a meal preferably in the evening in patients who need 50 mg of gemigliptin and who are currently treated with metformin 1000 mg or to be needed metformin 1000 mg.

For patients with inadequate glycemic control on metformin monotherapy or dual combination of metformin and sulfonylurea,

Zemimet® SR 50/1000 mg should generally be administered once daily with a meal preferably in the evening.

When switching from metformin immediate-release to Zemimet® SR 50/1000 mg, glycemic control should be closely monitored.

When used in combination with sulfonylurea, a lower dose of the sulfonylurea may be required to reduce the risk of hypoglycemia.

No studies have been performed specifically examining the safety and efficacy of

Zemimet® SR 50/1000 mg in patients previously treated with other oral anti-hyperglycemic agents and switched to Zemimet® SR 50/1000 mg. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

The maximum recommended daily dose of Zemimet® SR 50/1000 mg is 1 tablet.

Special populations

Renal impairment

An estimated glomerular filtration rate (eGFR) should be assessed before initiation of treatment with Zemimet® SR 50/1000 mg and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

It is not recommended to initiate treatment with Zemimet® SR 50/1000 mg in patients with an eGFR ≥ 30 mL/min/1.73 m^2 and eGFR < 45 mL/min/1.73m^2. If eGFR falls to levels persistently below 45 mL/min/1.73m^2 during treatment, assess the benefit and risk of continuing therapy. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of Zemimet® SR 50/1000 mg in patients with eGFR < 60 mL/min/1.73 m^2.

Hepatic Impairment

Since impaired hepatic function has been associated with some cases of lactic acidosis, Zemimet® SR 50/1000 mg should not be used in patients with hepatic impairment (see section 4.4 and 5.2).

Cardiac Impairment

There is limited clinical experience in patients with New York Heart Association (NYHA) Class I, II cardiac status in the case of gemigliptin. Therefore, Zemimet® SR 50/1000 mg should be used with caution in this population. Zemimet® SR 50/1000 mg should be avoided in patients with NYHA Class III, IV cardiac status (see section 4.4).

Elderly

Clinical experience with patients ≥ 65 years of age is limited and caution should be exercised when treating this population (see sections 4.3 and 4.4). Of the total number of patients (N= 1473) in Phase II and III clinical studies, 243 (16.5%) were 65 years and over. The efficacy and safety of gemigliptin were not different between young and elderly patients. However, Zemimet® SR 50/1000 mg should be used with caution in elderly patient because physiological functions including liver and kidney are usually decreased in this population. As metformin and gemigliptin are excreted by the kidney, and the impaired hepatic function is associated with some cases of metformin-related lactic acidosis, Zemimet® SR 50/1000 mg should be used with caution as age increases. Monitoring of renal and hepatic function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

Pediatric Population

Safety and effectiveness in children and adolescents below 18 years of age have not been established. No data are available.

Method of Administration

Zemimet® SR 50/1000 mg should generally be given once daily with a dinner meal to reduce the gastrointestinal adverse reactions associated with metformin.

Zemimet® SR 50/1000 mg should be swallowed as a whole and it must not be split, crushed, or chewed before swallowing.

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.

4.3 Contraindications

Zemimet® SR 50/1000 mg is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or a history of serious hypersensitivity reactions, i.e., angioedema or anaphylaxis, to another dipeptidyl peptidase-4 (DPP4) inhibitor (see sections 4.4 and 4.8);
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (eGFR < 30 mL/min/1.73 m^2);
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock,
  - intravascular administration of iodinated contrast agents (see section 4.4);
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock;
- hepatic impairment;
- acute alcohol intoxication, alcoholism;
- serious accidental injury

4.4 Special warnings and precautions for use

General

Zemimet® SR 50/1000 mg should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.Hypersensitive reaction

As Zemimet® SR 50/1000 mg contains gemigliptin and metformin, it should not be used in patients who have had any serious hypersensitivity reaction to a dipeptidyl peptidase 4 (DPP4) inhibitor or a biguanide.

Acute pancreatitis

Pancreatitis has been reported in patients taking gemigliptin. Therefore, patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Zemimet® SR 50/1000 mg 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
Patients receiving Zemimet® SR 50/1000 mg in combination with a sulfonylurea or with insulin may be at risk for hypoglycemia. Therefore, a reduction in the dose of the sulfonylurea or insulin maybe necessary.

Severe and disabling arthralgia
There have been post-marketing 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.

Lactic acidosis
Lactic acidosis, a rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (severe vomiting, diarrhea, fever or reduced fluid intake), Zemimet® SR 50/1000 mg should be temporarily discontinued and contact with a health care professional is recommended.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).
Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Zemimet® SR 50/1000 mg and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Diagnosis
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function
Metformin and gemigliptin are excreted by the kidney. Metformin-related lactic acidosis increases with the degree of impairment of renal function; serum creatinine concentrations should be determined regularly:

- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at or above the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating anti-hypertensive or diuretic therapy or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID) (see section 4.5).

eGFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). It is not recommended to initiate treatment with Zemimet® SR 50/1000 mg in patients with an eGFR $\geq$ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2. If eGFR falls to levels persistently below 45 mL/min/1.73m^2 during treatment, assess the benefit and risk of continuing therapy (see section 4.2 and 4.3).

Cardiac Impairment
There is limited clinical experience in patients with New York Heart Association (NYHA) Class I, II cardiac status in the case of gemigliptin. Therefore, Zemimet® SR 50/1000 mg should be used with caution in this population. Zemimet® SR 50/1000 mg should be avoided in patients with NYHA Class III, IV cardiac status (see section 4.2).

Surgery
As Zemimet® SR 50/1000 mg contains metformin, the treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia. Zemimet® SR 50/1000 mg should not usually be resumed earlier than 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Administration of iodinated contrast agent
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. Therefore, Zemimet® SR 50/1000 mg must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism (see section 4.8).

Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} serum levels which may cause peripheral neuropathy. Monitoring of the vitamin B_{12} level is recommended (see section 4.8).

Other precautions:

- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Co-administration with strong moderate CYP3A4 inducers such as rifampicin

(rifampin), phenytoin, carbamazepine and including moderate CYP3A4 inducers dexamethasone, rifabutin, and phenobarbital is not recommended (see section 4.5).

- The caution is required when co-administration with inhibitors of OCT2 to patients with renal impairment (see section 4.5).
- The tablet shells may be present in the feces. Patients should be advised that this is normal.
- Pregnant women or breastfeeding women should avoid taking Zemimet® SR 50/1000 mg (see section 4.6).
- Zemimet® SR 50/1000 mg should not be used with alcohol containing products.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Zemimet® SR 50/1000 mg. The following statements reflect the information available on the individual active substances.

Combinations not recommended

Alcohol

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin active substance of Zemimet® SR 50/1000 mg (see section 4.4). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore Zemimet® SR 50/1000 mg must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.4).

Combination requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary (see section 4.4).

Glucocorticoids

Glucocorticoids (given by systemic and local routes), beta-2 agonists, and diuretics have intrinsic hyperglycemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

ACE-inhibitors

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the anti-

hyperglycemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

In vitro assessment of interactions

Gemigliptin

The responsible enzyme for the metabolism of gemigliptin is CYP3A4. *In vitro* studies indicated that gemigliptin and its active metabolite are not inhibitors of CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4 and are not inducers of CYP1A2, 2C8, 2C9, 2C19, or 3A4. Therefore, gemigliptin is unlikely to cause interactions with other drugs that utilize these metabolic pathways but maybe affected by CYP3A inhibitors or inducers. Gemigliptin mildly inhibited P-gp mediated transport at a high concentration.

Effects of gemigliptin on other medicinal products

In clinical studies, gemigliptin did not meaningfully alter the pharmacokinetics of metformin, pioglitazone and glimepiride.

Metformin: Repeated co-administration of 50 mg gemigliptin with 2000 mg metformin 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, 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 did not meaningfully alter the pharmacokinetics of glimepiride at steady state. The effect of co-administration of gemigliptin on the AUC and C_{max} of glimepiride was less than 3%.

Effects of other medical products on gemigliptin

In clinical studies, metformin and pioglitazone did not meaningfully alter the pharmacokinetics of gemigliptin. Ketoconazole alters the pharmacokinetics of gemigliptin and its active metabolite but extended interaction was not considered clinically significant, and no dose adjustment is required. 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. The AUC and C_{max} of gemigliptin were decreased by 9% and 8%, respectively, and AUC and C_{max} of LC15-0636 were decreased by 5%.

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. The AUC of gemigliptin was increased by 6% while C_{max} was decreased by 3%. The AUC and C_{max} of active metabolite were increased by 3% and 9%, respectively.

Ketoconazole: Co-administration of multiple doses of 400 mg ketoconazole, 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, 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 (see sections 4.3 and 4.4).

Metformin

Phenprocoumon

Metformin may decrease the anti-coagulant effect of phenprocoumon. Therefore, a close monitoring of the INR is recommended.

Levothyroxine

Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated or stopped, and the dosage of metformin must be adjusted if necessary.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

4.6 Fertility, pregnancy and lactation

Pregnancy

No studies have been conducted with the combined active substances of Zemimet® SR 50/1000 mg.

There are no adequate and well-controlled studies in pregnant women with gemigliptin. Animal studies have shown reproductive toxicity at high doses of gemigliptin (see section 5.3). Because of the high safety margin, no relevant risk is suggested for pregnant women.

To date, no relevant epidemiological data are available with regard to the use of metformin. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see also section 5.3).

Zemimet® SR 50/1000 mg should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment with Zemimet® SR 50/1000 mg should be discontinued and switched to insulin treatment as soon as possible (see section 4.4).

Lactation

No studies have been conducted with the combined active substances of Zemimet® SR 50/1000 mg.

There is no information on excretion of gemigliptin or metformin into human milk. In animal studies performed with the individual active substances, both gemigliptin and metformin are excreted in the milk of lactating rats.

Zemimet® SR 50/1000 mg must therefore not be used in women who are breastfeeding (see section 4.4).

Fertility

No studies have been conducted with the combined active substances of Zemimet® SR 50/1000 mg.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with Zemimet® SR 50/1000 mg. However, patients should be alerted to the risk of hypoglycemia when Zemimet® SR 50/1000 mg is used in combination with other anti-diabetic medicinal products known to cause hypoglycemia (e.g. sulfonylureas).

4.8 Undesirable effects

There have been no therapeutic clinical trials conducted with Zemimet® SR 50/1000 mg tablets, however bioequivalence of Zemimet® SR 50/1000 mg with co-administered gemigliptin and metformin has been demonstrated.

Gemigliptin

Summary of the safety profile

There were 1468 patients with type 2 diabetes, including 1080 patients treated with gemigliptin, and 821 patients were treated with gemigliptin 50 mg, randomized in 5 double-blind and 1 open-label, controlled clinical safety and efficacy studies, conducted to evaluate the effects of gemigliptin on glycemic control.

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 most common (≥ 3% of patients) adverse reactions reported in the group treated with gemigliptin 50 mg once daily.

Table 1. Most common adverse reactions reported ≥ 3% of patients treated with gemigliptin 50 mg once daily in two placebo-controlled monotherapy studies (Regardless of investigator assessment of causality)

Name of adverse reaction	Gemigliptin 50 mg qd N = 126 (%)	Placebo N = 128 (%)
Arthralgia	6 (4.76)	0 (0)
Nasopharyngitis	4 (3.17)	8 (6.25)
Bacteriuria	4 (3.17)	1 (0.78)

The 24-week monotherapy study was extended through 52-week. The adverse events that increased more than 1% during the latter 28 weeks when compared with the first 24 weeks, regardless of assessment of causality, were nasopharyngitis (4.44% vs 6.1%), upper respiratory tract infection (1.1% vs 6.1%) and increase in blood creatine phosphokinase (2.22% vs 4.88%). No new adverse events were reported in more than 2 patients (2.44%) in latter 28 weeks.

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 most common (≥3% of patients) adverse reactions reported in this study.

Table 2. Most common adverse reactions reported in ≥ 3% of patients treated with gemigliptin 50 mg once daily in one active-controlled add-on combination study (Regardless of investigator assessment of causality)

Name of adverse reaction	Gemigliptin 50 mg, qd N = 140 (%)	Gemigliptin 25 mg, bid N = 141 (%)	Sitagliptin 100 mg, qd N = 140 (%)
Upper respiratory tract infection	8 (5.71)	4 (2.84)	6 (4.29)
Nasopharyngitis	7 (5)	11 (7.8)	4 (2.86)

Name of adverse reaction	Gemigliptin 50 mg, qd N = 140 (%)	Gemigliptin 25 mg, bid N = 141 (%)	Sitagliptin 100 mg, qd N = 140 (%)
Blood amylase increased	5 (3.57)	0 (0.00)	1 (0.71)
Lipase increased	5 (3.57)	6 (4.26)	3 (2.14)
Pyrexia	3 (2.14)	6 (4.26)	3 (2.14)

The 24-week add-on combination therapy was extended through 52-week with gemigliptin 50 mg once daily added on to stable dose of metformin. The adverse events that increased more than 1% during the latter 28 weeks when compared with the first 24 weeks, regardless of assessment of causality, were diarrhea (0.71 % vs 2.7%), urinary tract infection (0.71% vs 1.8%), hypoglycemia (0.71% vs 2.7%), dizziness (0.71% vs 3.6%) and nausea (1.43% vs 2.7%). The adverse events reported in more than 2 patients (1.8%) during the latter 28 weeks were asthenia (1.8%) and myalgia (1.8%).
No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with gemigliptin.

Gemigliptin 50 mg was added in patients inadequately controlled on their maximal tolerated dose of metformin and a glimepiride for 24 weeks. Table 3 summarizes the most common (≥3% of patients) adverse reactions reported in this study.

Table 3. Most common adverse reactions reported in ≥ 3% of patients treated in combination with metformin and glimepiride (Regardless of investigator assessment of causality)

Name of adverse reaction	Gemigliptin 50 mg N = 107 (%)	Placebo N = 111 (%)
Nasopharyngitis	7 (6.54)	5 (4.50)
Hypoglycemia	9 (8.41)	3 (2.70)
Dizziness	4 (3.74)	3 (2.70)

In a 24 weeks clinical trial that studied initial combination with metformin, gemigliptin 50 mg and metformin were individually administered and co-administered once daily. Table 4 summarizes the most common (≥3% of patients) adverse reactions reported in this study.

Table 4. Most common adverse reactions reported in ≥ 3% of patients treated with co-administration of metformin. (Regardless of investigator assessment of causality)

Name of adverse reaction	Gemigliptin 50 mg/ Metformin N = 141 (%)	Gemigliptin 50 mg N = 142 (%)	Metformin N = 150 (%)
Dyspepsia	13 (9.22)	7 (4.93)	10 (6.67)
Nasopharyngitis	12 (8.51)	19 (13.38)	18 (12)
Dizziness	7 (4.96)	3 (2.11)	1 (0.67)
Diarrhea	6 (4.26)	0 (0)	11 (7.33)
Dyslipidaemia	4 (2.84)	7 (4.93)	3 (2)
Headache	4 (2.84)	5 (3.52)	3 (2)

Name of adverse reaction	Gemigliptin 50 mg/ Metformin N = 141 (%)	Gemigliptin 50 mg N = 142 (%)	Metformin N = 150 (%)
Constipation	1 (0.71)	5 (3.52)	1 (0.67)
Backpain	0 (0)	1 (0.7)	8 (5.33)

A 12 weeks Phase 3b clinical trial was conducted with administration of gemigliptin 50 mg in active-controlled, randomized, open-label and parallel group design in order to evaluate MAGE (mean amplitude of glycemic excursions) and safety of gemigliptin and metformin initial combination therapy to the standard combination therapy (sitagliptin and metformin, glimepiride and metformin). Table 5 summarizes the most common (≥3% of patients) adverse reactions reported in this study.

Table 5. Most common adverse reactions reported in ≥ 3% of patients treated with co-administration of metformin. (Regardless of investigator assessment of causality)

Name of adverse reaction	Gemigliptin 50 mg/ Metformin N = 24 (%)	Sitagliptin 100 mg/ Metformin N = 23 (%)	Glimepiride 2 mg/ Metformin N = 22 (%)
Nasopharyngitis	1 (4.17)	1 (4.35)	0 (0.00)
Herpes simplex	0 (0.00)	1 (4.35)	0 (0.00)
Upper respiratory tract infection	1 (4.17)	0 (0.00)	0 (0.00)
Dizziness	0 (0.00)	1 (4.35)	1 (4.55)
Dysarthria	1 (4.17)	0 (0.00)	0 (0.00)
Mononeuropathy	0 (0.00)	1 (4.35)	0 (0.00)
Hypoglycaemia	0 (0.00)	0 (0.00)	2 (9.09)
Hypercholesterolaemia	1 (4.17)	0 (0.00)	0 (0.00)
Thyroid neoplasm	2 (8.33)	0 (0.00)	0 (0.00)
Hepatocellular carcinoma	0 (0.00)	1 (4.35)	0 (0.00)
Abdominal discomfort	0 (0.00)	0 (0.00)	1 (4.55)
Mouth ulceration	1 (4.17)	0 (0.00)	0 (0.00)
Stomatitis	1 (4.17)	0 (0.00)	0 (0.00)
Vomiting	1 (4.17)	0 (0.00)	0 (0.00)
Back pain	1 (4.17)	0 (0.00)	0 (0.00)
Intervertebral disc disorder	1 (4.17)	0 (0.00)	0 (0.00)
Neck pain	0 (0.00)	1 (4.35)	0 (0.00)
Spinal column stenosis	0 (0.00)	1 (4.35)	0 (0.00)
Visual acuity reduced	0 (0.00)	0 (0.00)	2 (9.09)
Benign prostatic hyperplasia	0 (0.00)	0 (0.00)	1 (4.55)

Name of adverse reaction	Gemigliptin 50 mg/ Metformin N = 24 (%)	Sitagliptin 100 mg/ Metformin N = 23 (%)	Glimepiride 2 mg/ Metformin N = 22 (%)
Sexual dysfunction	1 (4.17)	0 (0.00)	0 (0.00)
Oropharyngeal pain	0 (0.00)	0 (0.00)	1 (4.55)

The pooled safety analysis was performed in the subjects who had received gemigliptin at least once in above 6 randomized, controlled clinical studies.

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 (1.4% as compared to 0.8%).

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.

Table 6 presents adverse reactions which have been reported during 6 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), not known (cannot be estimated from the available data)

Table 6. Frequency of adverse reactions by system organ class and preferred term treated with gemigliptin

System Organ Class Adverse Reaction	Frequency N = 1080
Gastrointestinal disorders	
Abdominal discomfort	Uncommon
Abdominal pain upper	Uncommon
Constipation	Uncommon
Diarrhoea	Uncommon
Dyspepsia	Common
Eructation	Uncommon
Gastric disorder	Uncommon
Gastric ulcer	Uncommon
Gastritis haemorrhagic	Uncommon

System Organ Class Adverse Reaction	Frequency N = 1080
Gastrointestinal disorder	Uncommon
Hyperchlorhydria	Uncommon
Nausea	Uncommon
General disorders and administration site conditions	
Malaise	Uncommon
Swelling	Uncommon
Infections and infestations	
Asymptomatic bacteriuria	Uncommon
Nasopharyngitis	Uncommon
Upper respiratory tract infection	Uncommon
Urinary tract infection	Uncommon
Investigations	
Alanine aminotransferase abnormal	Uncommon
Alanine aminotransferase increased	Uncommon
Amylase increased	Uncommon
Blood creatine phosphokinase increased	Uncommon
Hepatic enzyme increased	Uncommon
Lipase increased	Uncommon
Pancreatic enzymes increased	Uncommon
Weight decreased	Uncommon
Metabolism and nutrition disorders	
Decreased appetite	Uncommon
Hypertriglyceridaemia	Uncommon
Hypoglycemia	Uncommon
Hypoglycemia unawareness	Uncommon
Musculoskeletal and connective tissue disorders	
Arthralgia	Uncommon
Myalgia	Uncommon
Nervous system disorders	
Diabetic neuropathy	Uncommon
Dizziness	Uncommon
Headache	Uncommon
Hypoaesthesia	Uncommon
Tension headache	Uncommon
Psychiatric disorders	
Insomnia	Uncommon
Reproductive system and breast disorders	
Vulvovaginal pruritus	Uncommon
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Uncommon
Skin and subcutaneous tissue disorders	
Photosensitivity reaction	Uncommon
Pruritus	Uncommon

System Organ Class Adverse Reaction	Frequency N = 1080
Pruritus generalized	Uncommon
Rash	Uncommon
Urticaria	Uncommon

Description of selected adverse reactions

Hypoglycemia

In six randomized controlled studies of gemigliptin, 15 patients (1.4%) reported hypoglycemia. The hypoglycemia experienced by patients in clinical trials was considered mostly of mild in intensity and patients fully recovered.

Hypersensitivity

In the active-controlled add-on combination study (gemigliptin as add-on to metformin therapy*)*, 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 (see section 4.3 and 4.4).

Metformin

Table 7 presents adverse reactions which have been reported during clinical studies and in postmarketing experience. The adverse reactions are listed by system organ class and by frequency category. 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 <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 7. Frequency of adverse reactions by system organ class treated with metformin

System organ class Adverse reaction	Frequency
Blood and lymphatic system disorders	
Hemolytic anemia	Not known
Metabolism and nutrition disorders	
Lactic acidosis[a]	Very rare
Vitamin B12 deficiency[b]	Very rare
Nervous system disorders	
Metallic taste	Common
Encephalopathy	Not known
Gastrointestinal disorders	
Gastrointestinal symptoms[c]	Very common
Skin and subcutaneous tissue disorders	
Erythema	Very rare
Photosensitivity	Not known
Investigations	
Reduction of thyrotropin level in patients with hypothyroidism	Not known
Hypomagnesemia in the context of diarrhea	Not known

[a] See section 4.4 Warnings and precautions.
[b] A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance. However, cases of peripheral neuropathy in patients with vitamin B12 deficiency have been reported in post-marketing experience (frequency not known) (see section 4.4).
[c] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Gemigliptin 50 mg/Metformin 1000 mg extended release

Summary of the safety profile

There were 182 patients with type 2 diabetes treated with a single concomitant dose of gemigliptin 50 mg and metformin 1000 mg extended release (2 tablets of metformin 500 mg extended release) in 2 double-blind and 1 open-label, controlled clinical safety and efficacy studies, conducted to evaluate the effects of gemigliptin on glycemic control.

The pooled safety analysis was performed in subjects who had received a single concomitant dose of gemigliptin 50 mg and metformin 1000 mg extended release in above 3 randomized, controlled clinical studies (one as an extension of an add-on combination to metformin, one as an initial combination with metformin, and the other as a phase 3b trial evaluating MAGE).

The overall incidence of adverse events in patients treated with gemigliptin 50 mg and metformin 1000 mg extended release was 49.5% (90/182). Among them, the incidence of adverse drug reactions was 7.7% (14/182).

Across all the clinical studies, there was no serious adverse drug reactions.

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.

Table 8 presents adverse reactions which have been reported during 3 randomized, controlled clinical studies.

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), not known (cannot be estimated from the available data)

Table 8. Frequency of adverse reactions by system organ class and preferred term treated with gemigliptin 50 mg and metformin 1000 mg extended release

System Organ Class Preferred Term (Adverse Reaction)	Frequency N = 182
Gastrointestinal disorders	
Constipation	Uncommon
Diarrhoea	Uncommon
Dyspepsia	Common
Gastric disorder	Uncommon

Gastritis haemorrhagic	Uncommon
Investigations	
Amylase increased	Common
Lipase increased	Common
Metabolism and nutrition disorders	
Decreased appetite	Uncommon
Hypoglycaemia	Uncommon
Hypoglycaemia unawareness	Uncommon
Nervous system disorders	
Dizziness	Uncommon

Description of selected adverse reactions

Hypoglycemia

In three randomized controlled studies of gemigliptin 50 mg and metformin 1000 mg, 4 patients (2.2%) reported hypoglycemia. Hypoglycemia unawareness was reported in 1 patient (0.5%). The hypoglycemia experienced by patients in clinical trials was considered mostly of mild in intensity and patients fully recovered.

Hypersensitivity

One patient (0.5%) receiving gemigliptin 50 mg and metformin 1000 mg extended release reported hypersensitivity, which was not related to gemigliptin.

In addition, two bioequivalence studies, one was conducted under fed conditions and the other was conducted under fasting conditions, included healthy volunteers administered a single dose of a fixed-dose combination of gemigliptin/metformin 50/1000 mg (Zemimet® SR 50/1000 mg) compared to a single concomitant dose of gemigliptin 50 mg and metformin 1000 mg extended release. In the first bioequivalence study conducted in healthy male volunteers under fed conditions, 10 adverse events were reported in 8 out of 24 subjects. The incidence of adverse events after receiving a single dose of Zemimet® SR 50/1000 mg was 8.33% for rhinorrhea, and 4.17% for alanine aminotransferase increase, aspartate aminotransferase increased, neutrophil count decreased, and upper abdominal discomfort, respectively. The incidence of adverse events after receiving a single concomitant dose of gemigliptin 50 mg and metformin 1000 mg extended release was 4.17% for neutrophil count decreased, creatine kinase increased, dizziness, and corneal abrasion, respectively.

In a second bioequivalence study conducted in healthy volunteers under fasting conditions, 8 adverse events were reported in 7 out of 37 subjects after receiving a single dose of Zemimet® SR 50/1000 mg and 11 post-dose adverse events were reported in 9 out of 37 subjects after receiving a single concomitant dose of gemigliptin 50 mg and metformin 1000 mg extended release. The most reported adverse event post-dose was asymptomatic hypoglycemia which occurred 10.81% and 21.62% after receiving a single dose of Zemimet® SR 50/1000 mg and a single concomitant dose of gemigliptin 50 mg and metformin 1000 mg extended release, respectively. Other reported adverse events after receiving a single dose of Zemimet® SR 50/1000 mg were hemoglobin and hematocrit decreased (2.70%), diarrhea (2.70%), loose stool (2.70%) and AST and ALT

increased (2.70%), and other reported adverse events after receiving a single concomitant dose of gemigliptin 50 mg and metformin 1000 mg extended release were abnormal ECG (2.70%), nausea (2.70%), and dizziness (2.70%).

In a randomized, open-label, single oral dose, one-treatment, two-period, two-sequence, crossover food-effect bioavailability study under fed and fasting conditions in healthy Thai volunteers, 40 post-dose adverse events were reported in 19 out of 26 subjects receiving Zemimet® SR 50/1000 mg. The most reported adverse event after single dose administration of Zemimet® SR 50/1000 mg was asymptomatic hypoglycemia which occurred 55.00% and 60.00% under fasting and fed conditions, respectively. Other reported adverse events after single dose administration of Zemimet® SR 50/1000 mg under fasting conditions were vomiting (15.00%), dizziness (10.00%), nausea (5.00%), WBC count increased (5.00%), hyperglycemia (5.00%) and symptomatic hypoglycemia (5.00%). Other reported adverse events after single dose administration of Zemimet® SR 50/1000 mg under fed conditions were hemoglobin and hematocrit decreased (15.00%), dizziness (10.00%), diarrhea (5.00%), nausea (5.00%) and faintness (5.00%).

4.9 Overdose

No data are available with regard to overdose of Zemimet® SR 50/1000 mg.

Gemigliptin

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.

Metformin

Hypoglycemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin may lead to lactic acidosis. The most effective method to remove lactate and metformin is haemodialysis.

Pancreatitis may occur in the context of a metformin overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD18.

Mechanism of action and pharmacodynamic effects

Zemimet® SR 50/1000 mg combines two anti-hyperglycemic medicinal products with complementary mechanisms of action to improve glycemic control in patients with type 2

diabetes: gemigliptin tartrate sesquihydrate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Gemigliptin

Mechanism of Action

Gemigliptin 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 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-9 and DPP-8, respectively.

Clinical Efficacy and Safety

The benefit of administering gemigliptin in patients with type 2 diabetes and the risk associated with this treatment has been evaluated in the clinical program conducted in total 1473 subjects randomized in 6 clinical trials.

Gemigliptin dose finding

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 50 mg, 100 mg and 200 mg, respectively.

Monotherapy

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% [95% 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 was evaluated in an 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<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 was evaluated in a placebo-controlled Phase III study of 24 week duration. Analysis of covariance (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 least square 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 group was demonstrated.

Gemigliptin and metformin as initial therapy
The efficacy and safety of gemigliptin initial combination therapy with metformin was evaluated in an active-controlled Phase III study of 24 week duration. For the change of HbA1c from baseline at Week 24, analysis of covariance was performed. As a result, 95% CI for between group difference in least square 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 CI were less than zero (p<0.001), confirming superiority of the combination therapy group.

Glycemic variability of gemigliptin versus sitagliptin or glimepiride
The efficacy of gemigliptin on MAGE (mean amplitude of glycemic excursions) and safety of initial combination therapy of gemigliptin versus sitagliptin or glimepiride with metformin in patients with type 2 diabetes was evaluated in a multicenter, randomized, active-controlled, parallel group, open-label, exploratory study. The change in MAGE at Week 12 was -43.11mg/dL, -38.27mg/dL and -21.74mg/dL in the gemigliptin and metformin group, sitagliptin and metformin group and glimepiride and metformin group, respectively. In the test result between the groups, DPP-4 inhibitors, i.e., the gemigliptin and metformin group and sitagliptin and metformin group, reduced the MAGE compared to sulfonylurea, i.e., glimepiride and metformin group (gemigliptin: p=0.0306, sitagliptin: p=0.0292).

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.

<u>Metformin</u>
Mechanism of action

Metformin is a biguanide with anti-hyperglycemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycemia.

Metformin may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

Clinical efficacy and safety
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

5.2 Pharmacokinetic properties

Zemimet® SR 50/1000 mg

A bioequivalence study in healthy subjects demonstrated that the Zemimet® SR 50/1000 mg combination tablets are bioequivalent to co-administration of gemigliptin and metformin hydrochloride as individual tablets.

The effects of food on pharmacokinetics of Zemimet® SR 50/1000 mg combination

tablets were similar to the known food effects of gemigliptin or metformin as individual tablets.

Absorption
After administration of Zemimet® SR 50/1000 mg as a single oral dose to healthy male subjects under fed conditions, the T_{max} for gemigliptin is reached in 3 hr, C_{max} and AUC_{last} for gemigliptin were 67.78 ng/mL and 707.57 ng•hr/mL, respectively. The T_{max} for metformin is reached in 7 hr, C_{max} and AUC_{last} for metformin were 1,297.09 ng/mL and 14,726.8 ng•hr/mL, respectively.

After administration of Zemimet® SR 50/1000 mg as a single oral dose to healthy subjects under fasting conditions, the T_{max} for gemigliptin is reached in 3 hr. C_{max} and AUC_{last} for gemigliptin were 59.3046 ng/mL and 807.76 ng•hr/mL, respectively. The T_{max} for metformin is reached in 4 hr, C_{max} and AUC_{last} for metformin were 1,301.1621 ng/mL and 10,179.13 ng•hr/mL, respectively.

Effect of Food
After administration of Zemimet® SR 50/1000 mg as a single-dose to healthy subjects under fasting and fed conditions, for gemigliptin and metformin, the values of C_{max} were 41% and 39% higher in fed conditions than in fasting conditions, respectively. However, the values of AUC_{last} was not significantly different between fasting and fed conditions, and also the 90% confidence intervals were within bioequivalence ranges. Hence, a weak pharmacokinetic interaction of Zemimet® SR tab 50/1000 mg by food effect was observed, however, the interaction is not clinically significant.

The following statements reflect the pharmacokinetic properties of the individual active substances of Zemimet® SR 50/1000 mg.
Gemigliptin
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 clinical 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. When co-administration of a high-fat meal with gemigliptin, food slightly delayed the absorption of gemigliptin, decreased the C_{max} by 39% but did not affect the AUC. These changes were not considered to be clinically meaningful.

Distribution
In vitro human plasma protein binding is 29% for gemigliptin and 35% ~ 48 % for the metabolites including the 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 9% ~ 18% 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 of CYP1A2, 2C8, 2C9, 2C19, or 3A4.

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.

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.

<u>Metformin</u>

Absorption
After an oral dose of metformin, T_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in feces was 20-30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed

that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/mL. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 μg/mL, even at maximum doses.

Interaction with food
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63 – 276 L.

Biotransformation
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

No animal studies have been conducted with Zemimet® SR 50/1000 mg. Potential toxicity and reversibility to the combination of gemigliptin and metformin was evaluated in rats administered co-suspended formulation.

In the oral rat single-dose study, the approximate lethal dose levels were considered to be greater than 150 mg/kg and 1500 mg/kg for gemigliptin and metformin, respectively.

In 3-month toxicity studies in which rats were treated with either metformin or gemigliptin alone, or a combination of metformin and gemigliptin, no additional toxicity was observed from the combination. The NOAEL in these studies was observed at exposures to gemigliptin of approximately 23~26 times the human exposure (50 mg) and to metformin of approximately 13~14 times the human exposure (1000 mg).

The following data are findings in studies performed with gemigliptin or metformin individually.

<u>Gemigliptin</u>
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, 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.

In animal studies, gemigliptin was excreted at a ratio of 1: 4~10 in plasma and milk in rats. Therefore, Zemimet® SR 50/1000 mg should not be administered in nursing woman.

Metformin
Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline Cellulose (Type 102)
Croscarmellose Sodium
Stearyl Fumarate Sodium
Magnesium Stearate
Polyvinyl Acetate Aqueous Dispersion 30%
Hypromellose
Opadry II 85F34790

Film coating
Polyvinyl Alcohol
Titanium Dioxide
Polyethylene Glycol 3350
Talc
Red Iron Oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Opaque blisters (PVC/PVDC and aluminum). A pack of 28 or 56 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. MARKETING AUTHORISATION HOLDER
LG Chem Life Sciences (Thailand), Ltd.
87/2 CRC Tower, All Seasons Place, 19th Floor,
Wireless Road, Lumpini, Pathumwan, Bangkok 10330

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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March 29, 2022