Zemidapa 50/10 mg Film-Coated Tablet
(Gemigliptin Tartrate Sesquihydrate/Dapagliflozin)

1. NAME OF THE MEDICINAL PRODUCT
Zemidapa 50/10 mg Film-Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains gemigliptin tartrate sesquihydrate, equivalent to 50 mg of gemigliptin, and 10 mg of dapagliflozin (amorphous).

3. PHARMACEUTICAL FORM
Zemidapa is round, bright brown, film-coated tablet, debossed with a “LG” and a wave pattern on one side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
Zemidapa is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:
- to improve glycaemic control when metformin and one of the monocomponents of Zemidapa do not provide adequate glycaemic control
- when already being treated with the free combination of dapagliflozin and gemigliptin

4.2 Posology and method of administration
Posology
Adults
The recommended dose is one tablet once daily.
Special populations
Renal impairment
The efficacy and safety of Zemidapa is dependent on renal function, and renal function should be evaluated prior to initiation of Zemidapa and periodically thereafter.
- For patients with eGFR $\geq$ 45 mL/min/1.73m^2, no dose adjustment is required.
- For patients with eGFR < 45 mL/min/1.73m^2, Zemidapa is not recommended.

Hepatic impairment
No dose adjustment is required for patient with mild or moderate hepatic impairment. The safety and efficacy of Zemidapa in patients with severe hepatic impairment have not yet been established.
Cardiac impairment
There is limited experience in patients with New York Heart Association (NYHA) Class I, II cardiac status in the case of gemigliptin. Therefore, Zemidapa should be used with caution in this population. Due to limited clinical experience in patients with NYHA Class III, IV cardiac status in the case of gemigliptin, the use of Zemidapa is not recommended in this population.
Elderly
Caution should be used in elderly patient because physiological functions including liver and kidney are usually decreased in this population.
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
Zemidapa can be taken orally once daily with or without food.

4.3 Contraindications
Zemidapa is contraindicated in patients with/on:
- hypersensitivity to the active substances or to any of the excipients listed at the end of this leaflet, or a history of serious hypersensitivity reactions, i.e., angioedema or anaphylaxis, to another dipeptidyl peptidase-4 (DPP-4) inhibitor or sodium glucose cotransporter (SGLT) 2 inhibitor;
- type 1 diabetes or diabetic ketoacidosis
- rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
- hemodialysis

4.4 Special warnings and precautions for use

Gemigliptin

Hepatic impairment

Zemidapa should be used with caution as there is no experience in clinical studies in patients with severe hepatic impairment in the case of gemigliptin. There is limited experience in clinical studies in patients with hepatic impairment in the case of dapagliflozin. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

Cardiac impairment

There is limited clinical experience in patients with NYHA Class I, II cardiac status in the case of gemigliptin. Therefore, Zemidapa should be used with caution in this population. Zemidapa should be avoided in patients with NYHA Class III, IV cardiac status.

Acute pancreatitis

Pancreatitis has been reported in patients taking DPP-4 inhibitors including gemigliptin. Therefore, patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Zemidapa 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 Zemidapa 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.

Bullous pemphigoid

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

Hypersensitive reactions

This medicinal product must not be used in patients who have had any serious hypersensitivity reaction to a DPP-4 inhibitor or a SGLT2 inhibitor.

Severe hypersensitivity reactions have been reported in patients treated with gemigliptin post marketing, including Stevens-Johnson syndrome. If serious hypersensitivity reaction is suspected, this drug should be discontinued, other potential causes of the reaction should be identified, and administer other diabetes therapies.

Dapagliflozin

Use in patients at risk for volume depletion and/or hypotension

Due to dapagliflozin's mechanism of action, this medicinal product increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with this medicinal product is recommended for patients who develop volume depletion until the depletion is corrected.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/litres (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of dapagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with this medicinal product should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.
Before initiating treatment with this medicinal product, factors in the patient history that may predispose to ketoacidosis should be considered.
Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.
Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.
The safety and efficacy of the Zemidapa in patients with type 1 diabetes have not been established and it should not be used for treatment of patients with type 1 diabetes. In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency.
Genital mycotic infections
Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.
Elderly
Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.
Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.
There are insufficient data to draw conclusions regarding exposure in patients ≥ 70 years old.
Urinary laboratory assessments
Due to its mechanism of action, patients taking dapagliflozin will test positive for glucose in their urine.
Urosepsis and Pyelonephritis
Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.
Use with medications known to cause hypoglycemia
Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with dapagliflozin in patients with type 2 diabetes mellitus.
SGLT-2 inhibitors such as dapagliflozin may worsen the condition due to an increase in urinary volume in patients with underlying bladder disorders, requiring caution when prescribing to these patients.
Body weight loss
In placebo-controlled study of 24-week duration in subjects with inadequately controlled type 2 diabetes mellitus, dapagliflozin resulted in greater body weight reduction from baseline compared with placebo (-3.16kg and -2.19kg, respectively).
Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.
Necrotising fasciitis of the perineum (Fournier's gangrene)
Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.
Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Zemidapa should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

4.5 Interaction with other medicinal products and other forms of interaction
Gemigliptin

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 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. *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 interaction
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 area under the curve (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.
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 25 mg 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 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.
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.
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.

Dapagliflozin
Pharmacodynamics interactions
Diuretics: Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension
Insulin and insulin secretagogues: Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with dapagliflozin in patients with type 2 diabetes mellitus.

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolized by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycemic control is advised.

Lithium

Concomitant use of dapagliflozin and lithium may lead to reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

Other interactions

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of dapagliflozin have not been studied.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

No studies have been conducted with the combined active substances of Zemidapa. Studies in animals with gemigliptin have shown that gemigliptin was transferred to placenta and up to 48.1% and 1.6% were detected in amniotic fluids when administered to pregnant rats and rabbits, respectively, at 2 hours post dose. Studies with dapagliflozin in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, Zemidapa should not be used during pregnancy. If pregnancy is detected, treatment with Zemidapa should be discontinued.

Breast-feeding

No studies have been conducted with the combined active substances of Zemidapa. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in breast-feeding offspring. A risk to the newborns/infants cannot be excluded. Zemidapa should not be used while breast-feeding.

Fertility

No studies have been conducted with the combined active substances of Zemidapa. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested. Animal studies with gemigliptin 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 Zemidapa. However, patients should be alerted to the risk of hypoglycemia when Zemidapa is used in combination with other anti-diabetic medicinal products known to cause hypoglycemia (e.g. sulfonylureas).

4.8 Undesirable effects

For further information on adverse effects associated with the gemigliptin and dapagliflozin refer to the appropriate individual Product Information document.

Summary of the safety profile

In a 24-week study in type 2 diabetes mellitus patients who had inadequate blood glucose control in combination with metformin and dapagliflozin, gemigliptin 50 mg or placebo was administered once daily as an add-on combination. Table 1 summarizes the most common (≥1.0% of patients) adverse events reported in this study.

Table 1. Most common adverse events reported in ≥ 1.0% of patients treated with gemigliptin as add-on to metformin and dapagliflozin (Regardless of Investigator Assessment of Causality)

Name of adverse event	Gemigliptin 50mg N=159 (%)	Placebo N=154 (%)
Investigations		
Lipase increased	4 (2.52%)	2 (1.30%)
Gastrointestinal disorders		
Chronic gastritis	3 (1.89%)	0
Gastritis	2 (1.26%)	1 (0.65%)
Large intestine polyp	2 (1.26%)	0
Dyspepsia	1 (0.63%)	2 (1.30%)
Infections and infestations		
Urinary tract infection	3 (1.89%)	0
Gingivitis	2 (1.26%)	0
Nervous system disorders		
Dizziness	3 (1.89%)	1 (0.65%)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (1.26%)	0
Renal and urinary disorders		
Diabetic nephropathy	2 (1.26%)	2 (1.30%)
Skin and subcutaneous tissue disorders		
Urticaria	2 (1.26%)	0

The 24-week add-on combination therapy was extended through 52-week with gemigliptin 50 mg added on to stable dose of metformin and dapagliflozin. The new adverse events that occurred in 2 or more patients (1.30%) during the latter 28 weeks when compared with the first 24 weeks, regardless of assessment of causality, were hyperglycemia (0% vs 1.30%) and headache (0% vs. 1.30%).

In a 24-week study in type 2 diabetes mellitus patients who had inadequate blood glucose control on metformin alone, dual add-on therapy with gemigliptin 50 mg and dapagliflozin 10 mg or each add-on therapy with gemigliptin 50 mg or dapagliflozin 10 mg was administered once daily. Table 2 summarizes the most common (≥1.0% of patients) adverse events reported in this study.

Table 2. Most common adverse events reported in ≥ 1.0% of patients treated with add-on therapy with gemigliptin and dapagliflozin on metformin alone (Regardless of Investigator Assessment of Causality)

System Organ Class Preferred Term	Gemigliptin 50 mg + Dapagliflozin 10 mg (N=155)	Gemigliptin 50 mg (N=156)	Dapagliflozin 10 mg (N=156)
Metabolism and nutrition disorders			
Hypoglycaemia	4 (2.58%)	3 (1.92%)	1 (0.64%)
Gastrointestinal disorders			
Constipation	3 (1.94%)	2 (1.28%)	1 (0.64%)
Dyspepsia	2 (1.29%)	2 (1.28%)	3 (1.92%)
Gastrooesophageal reflux disease	1 (0.65%)	2 (1.28%)	1 (0.64%)
Nausea	1 (0.65%)	2 (1.28%)	0
Epigastric discomfort	0	2 (1.28%)	0
Gastritis erosive	0	2 (1.28%)	0
Infections and infestations			
COVID-19	3 (1.94%)	4 (2.56%)	2 (1.28%)
Cystitis	0	2 (1.28%)	1 (0.64%)
Nasopharyngitis	0	0	2 (1.28%)
Upper respiratory tract	0	0	2 (1.28%)

infection			
Skin and subcutaneous tissue disorders			
Pruritus	3 (1.94%)	1 (0.64%)	1 (0.64%)
Musculoskeletal and connective tissue disorders			
Myalgia	2 (1.29%)	1 (0.64%)	1 (0.64%)
Back pain	2 (1.29%)	1 (0.64%)	0
Pain in extremity	2 (1.29%)	0	0
Arthralgia	1 (0.65%)	3 (1.92%)	3 (1.92%)
Reproductive system and breast disorders			
Pruritus genital	2 (1.29%)	0	3 (1.92%)
Vulvovaginal pruritus	1 (0.65%)	0	2 (1.28%)
Nervous system disorders			
Dizziness	1 (0.65%)	2 (1.28%)	0
Headache	0	1 (0.64%)	2 (1.28%)
Psychiatric disorders			
Insomnia	1 (0.65%)	2 (1.28%)	0
Renal and urinary disorders			
Haematuria	0	3 (1.92%)	0
Pollakiuria	0	2 (1.28%)	0
Investigations			
Alanine aminotransferase increased	0	2 (1.28%)	3 (1.92%)
Aspartate aminotransferase increased	0	1 (0.64%)	2 (1.28%)
Weight decreased	0	0	3 (1.92%)
Blood creatine phosphokinase increased	0	0	2 (1.28%)
General disorders and administration site conditions			
Chest pain	0	2 (1.28%)	1 (0.64%)
Hepatobiliary disorders			
Hepatic steatosis	0	2 (1.28%)	0

Description of selected adverse reactions

Hypoglycemia

In a 24-week study in which gemigliptin 50 mg or placebo was administered once daily in patients with combination of metformin and dapagliflozin, hypoglycemia was reported in 1 patient (0.63%) in the gemigliptin 50 mg group. The hypoglycemia experienced by the patient in the clinical trial was at level 1 (hypoglycemic alert value) in severity and fully recovered, which was not related to gemigliptin 50 mg administration. During the latter 28 weeks in the extended 52-week study of gemigliptin 50 mg, 2 patients (1.30%) reported hypoglycemia. Two patients (1 patient (1 case) with level 1 and 1 patient (1 case) with level 2 (clinically significant hypoglycemia)) recovered during the clinical trial, which was not related to gemigliptin 50 mg administration.

In a 24-week study in which dual add-on therapy with gemigliptin 50 mg and dapagliflozin 10 mg or each add-on therapy with gemigliptin 50 mg or dapagliflozin 10 mg was administered once daily in patients on metformin, hypoglycemia was reported in 4 subjects (2.58%) in the dual add on therapy with gemigliptin 50 mg and dapagliflozin 10 mg group. All of the hypoglycemic levels were at level 1 (hypoglycemic alert value), and all of which except 1 case were reported to be related to gemigliptin 50 mg and dapagliflozin 10 mg. but all of the 4 subjects were recovered during the study period.

4.9 Overdose

No data are available with regard to overdose of Zemidapa.

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.

Dapagliflozin

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum

recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD30

Mechanism of action and pharmacodynamic effects

Zemidapa 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 DPP-4 inhibitor, and dapagliflozin, a SGLT 2 inhibitor.

Clinical efficacy and safety

Glycemic control

Gemigliptin add-on to metformin and dapagliflozin combination therapy

In a 24-week, multicenter, randomized, placebo-controlled, parallel-group, double-blind study, gemigliptin 50 mg was compared to placebo once daily as add-on therapy in subjects with inadequate glycemic control type 2 diabetes mellitus (7.0% ≤ HbA1c ≤ 11.0%) in combination with metformin (≥ 1,000 mg/day) and dapagliflozin (10 mg/day). At week 24, the adjusted mean change in HbA1c from baseline was −0.86% for the gemigliptin 50 mg group and −0.20% for the placebo group. Gemigliptin 50 mg resulted in statistically significant (p-value <0.0001) reductions in HbA1c compared to placebo at week 24 (adjusted mean change difference: −0.66% (95% CI: −0.80%, −0.52%).

Dual add-on therapy with gemigliptin and dapagliflozin in patients with inadequate glycemic control on metformin

In a 24-week, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study, dual add-on therapy with gemigliptin 50 mg and dapagliflozin 10 mg was compared to each add-on therapy with gemigliptin 50 mg or dapagliflozin 10 mg once daily in subjects with inadequate glycemic control type 2 diabetes mellitus (7.0% ≤ HbA1c ≤ 11.0%) on metformin (≥1,000 mg/day) alone regarding efficacy and safety.

At week 24, the adjusted mean change in HbA1c from baseline were -1.34%, -0.90% and -0.78%, respectively, in the gemigliptin and dapagliflozin group, in either gemigliptin or dapagliflozin group. The dual add-on therapy with gemigliptin and dapagliflozin resulted in statistically significant (*p*-value <0.0001) reductions in HbA1c compared to the add-on therapy with either gemigliptin or dapagliflozin at week 24 (adjusted mean change difference: -0.44% (95% CI: -0.58%, -0.31%).

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

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.

Dapagliflozin

Mechanism of action

Dapagliflozin is a reversible competitive inhibitor of sodium glucose co-transporter 2 (SGLT2) with nanomolar potency that improves glycaemic control in patients with type 2 diabetes mellitus and provides cardio renal benefits. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and

osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. Secondary effects of SGLT2 inhibition with dapagliflozin also include a modest reduction in blood pressure, reduction in body weight, and an increase in haematocrit.
The cardio-renal benefits of dapagliflozin are not solely dependent on the blood glucose lowering effect and not limited to patients with diabetes. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms underlying the cardio-renal beneficial effects of dapagliflozin. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.
The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging.
SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is approximately 1000-3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.
Pharmacodynamic effects
Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day dose of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.
This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.
Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 18.3 to 48.3 μmol/L.

5.2 Pharmacokinetic properties
Zemidapa
A bioequivalence study in healthy subjects demonstrated that the Zemidapa combination tablets are bioequivalent to co-administration of gemigliptin and dapagliflozin as individual tablets.
The effects of food on pharmacokinetics of Zemidapa combination tablets were similar to the known food effects of gemigliptin or dapagliflozin as individual tablets.

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 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 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. 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.

<u>Dapagliflozin</u>

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment).

Metabolism

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide. Dapagliflozin 3-O-glucuronide, with a molar plasma AUC 52% higher than that of dapagliflozin itself at the clinical dose, is an inactive metabolite and does not contribute to the glucose lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP mediated metabolism was a minor clearance pathway in humans.

Excretion

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After oral administration of 50 mg [^{14}C] dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug. The mean plasma terminal half-life ($t^{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects.

Renal impairment

Dapagliflozin should not be used in patients with eGFR persistently <45 mL/min/1.73 m^2. At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate or severe renal impairment

(as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60% and 87% higher, respectively, than those of patients with type 2 diabetes and normal renal function. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The renal glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-h urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known.

Hepatic impairment

A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

Elderly

The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group [90% CI: 87.9, 92.2%] and 25% higher in elderly patients compared to the reference group [90% CI: 123, 129%]. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients >70 years old.

Gender

Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUCss in females (n=619) was estimated to be 22% higher than in males (n=634) (90% CI; 117,124).

Race

Race (White, Black [African descent], or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to Whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures [90% CI range; 3.7% lower, 1% higher]. Compared to Whites, Black (African descent) subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures [90% CI range; 7.7% lower, 3.7% lower].

Body Mass Index

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high body weight subjects (≥120 kg, n=91) were estimated to be 78.3% [90% CI: 78.2, 83.2%] of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in patients with type 2 diabetes mellitus with high body weight (≥120 kg) is recommended.

Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29% higher than subjects with the reference group body weight. This difference is considered to be small and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in patients with type 2 diabetes mellitus with low body weight (<50 kg) is recommended.

5.3 Preclinical safety data

No animal studies have been conducted with Zemidapa.

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

Dapagliflozin
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core
Microcrystalline Cellulose (Type 102)
Lactose Anhydrous
Croscarmellose Sodium
Sodium stearyl Fumarate
Opadry II 85F665000 Brown
Film coating
Polyvinyl Alcohol
Titanium Dioxide
Polyethylene Glycol 3350
Talc
Yellow Iron Oxide
Red Iron Oxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
1) Keep out of the reach of children.
2) Store in the originally purchased container. Placing in container other than the ones provided by the manufacturer may lead to drug misuse or affect the quality of the drug product.

6.5 Package Quantity
Nylon/Alu/PVC Aluminum Foil Pack x 14's (Box of 28's)

6.6 Storage Condition
Store below 30°C. Store in tight container. Do not freeze.

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

7. MANUFACTURER
LG Chem, Ltd.
151, Osongsaengmyeong 1-ro,
Osong-eup, Heungdeok-gu,
Cheongju-si, Chungcheongbuk-do,
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PRODUCT REGISTRATION HOLDER
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Seksyen 7, 40000 Shah Alam
Malaysia

8. DATE OF REVISION
24-Jun-2025