Evogliptin

Suganon®

5mg Film-Coated Tablet
Anti-Diabetic (DPP-4 **I**nhibitor)

Rx

PRODUCT DESCRIPTION:
Pink, round, film-coated tablet

FORMULATION:
Each film-coated tablet contains:
Evogliptin tartrate …….....……6.869 mg
(5mg as Evogliptin)

PHARMACODYNAMICS:
Evogliptin is a member of a class of oral anti-hyperglycaemic agents called DPP-4 inhibitors. Evogliptin selectively inhibits the activity of DPP-4 by reversibly binding to DPP-4, an enzyme that inactivates incretin hormones such as GLP-1 (Glucagon-like peptide-1). Evogliptin dose-dependently inhibits the activity of DPP-4, thereby blocking GLP-1 from being inactivated by DPP-4, increasing the concentration of endogenous active GLP-1 and prolonging its action, and improves glucose-dependent insulin secretion in pancreatic beta cells by GLP- 1, and suppresses increase in blood sugar.The IC50 of evogliptin against recombinant human DPP-4 was 0.980 nM, and the inhibitory constant (Ki) was 0.525 nM. Compared to DPP-8 and DPP-9, evogliptin showed high selectivity of about 7,898 times and about 6,058 times, respectively, to DPP-4 (in vitro).

PHARMACOKINETICS:
Absorption
After a single oral administration of evogliptin 5mg in fasting state, the maximum blood concentration reached in about 4 hours. In repeated oral administration, steady state reached in 48 hours after the first administration. Comparing the bioavailability of evogliptin 10 mg between fast state and fed state (high-fat meal), it was found that there is no food effect in terms of bioavailability of evogliptin.
Distribution
Evogliptin is widely distributed to tissues after administration. When reacting evogliptin in heparin-treated plasma of mice, rats, dogs, and humans, the plasma protein binding rates of evogliptin were about 63%, about 25%, about 43%, and about 46%, respectively; binding rates were not related to the concentration of evogliptin in the reacted range (100-1,000 ng/mL). In pregnant female rats and rabbits or lactating rats, the concentration of evogliptin in fetal plasma or milk increased maternal exposure dependently.
Metabolism
Metabolic stability of evogliptin was confirmed in in vitro tests using liver microsomes or hepatocytes. Evogliptin circulates in plasma mainly as parent, and the major metabolites are M16, M8, M7, and M13. The main metabolic pathways were hydroxylation (M7, M8), sulfation (M13) by CYP3A4 and glucuronidation by UGT2B7 (M7 → M16). The major metabolites M16, M8, M7, and M13 were all identified as active forms, but showed at least 110 times lower DPP-4 inhibitory activity compared to the evogliptin parent. Therefore, considering the blood exposure level and inhibitory activity of major metabolites, it is very unlikely that the metabolites will reach effective blood levels.
Excretion
After a single oral administration of evogliptin 5mg in fasting state, the mean half-life (t1/2) of elimination was about 32.5 hours. After a single oral administration of [14C]-evogliptin 5mg in fasting state, 74.9% to 93.9% were excreted through urine and feces, respectively. The average excretion rates in urine and feces were 46.1% and 42.8%, respectively, and the main excretory body was the evogliptin parent.

Characteristics in patients
I. Hepatic impairment
After a single oral administration of evogliptin 5 mg, the exposure of evogliptin, evaluated by Cmax and AUClast, was observed similarly between patients with mild liver dysfunction (Child-Pugh A) and healthy adults with normal liver function when matching with sex, age and weight. In patients with moderate hepatic dysfunction (Child-Pugh B), Cmax and AUClast were about 1.37 times and about 1.44 times, respectively, compared to healthy adults with normal liver function. However, these pharmacokinetic differences are not considered to have a clinically significant effect.

II. Renal impairment
After a single oral administration of evogliptin 5mg, patients with mild renal impairment (60 ≤MDRD eGFR(mL/min/1.73m2) <90) had blood exposure similar to those of healthy adults with normal renal function (90 ≤ MDRD eGFR(mL/min/1.73m2)). In patients with moderate renal impairment (30 ≤ MDRD eGFR(mL/min/1.73m2)<60) and patients with severe renal impairment (15 ≤MDRD eGFR(mL/min/1.73m2)<30), the AUC was about 1.8 times and about 1.98 times, and Cmax about 1.32 times and about 1.52 times, respectively, compared to healthy adults with normal renal function. However, these pharmacokinetic differences are not considered to have a clinically significant effect.

After a single oral administration of evogliptin 5 mg before and after hemodialysis in patients with end-stage renal disease undergoing hemodialysis (MDRD eGFR(mL/min/1.73m2<15), the AUC was about 1.30 times (administration before dialysis) and about 1.39 times (administration after dialysis), and Cmax about 0.88 times (administration before dialysis) and about 1.20 times (administration after dialysis), respectively, compared to healthy adults with normal renal function (90 MDRD eGFR(mL/min/1.73m2)). The AUC was about 0.95 times and Cmax was about 0.73 times, when administered before hemodialysis compared to when administered after hemodialysis. These pharmacokinetic differences are not considered to have a clinically significant effect.

INDICATION:
Evogliptin (Suganon®) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.
1. Monotherapy
2. Combination therapy

DOSAGE AND MODE OF ADMINISTRATION:
The recommended dose of Evogliptin (Suganon®) is 5 mg once daily as monotherapy or combination therapy, and the maximum daily dose of Evogliptin (Suganon®) is 5 mg. Evogliptin (Suganon®) can be taken with or without food. Dosage and administration adjustment is not needed in patients with mild to moderate hepatic impairment.

CONTRAINDICATION:
1.) Patients who show serious hypersensitivity such as anaphylaxis or angioedema to Evogliptin (Suganon®) or other dipeptidyl peptidase 4 (DPP-4) inhibitors.
2.) Patients with type I diabetes or diabetic ketoacidosis.

PRECAUTION:
1.) Concomitant administration with drugs known to cause hypoglycemia: Insulin secretagogues such as insulin or sulfonylurea may cause hypoglycemia. Thus, lowering the dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia in case of concomitant administration with Evogliptin (Suganon®).
2.) Severe and disabling joint pain - Severe and disabling joint pain has been reported in patients administering other DPP-4 inhibitors in post-marketing studies. The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients experienced relief of symptoms upon discontinuation of the medication. Some patients had a recurrence of severe joint pain when restarted on either their original DPP-4 inhibitor medication or another DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue Evogliptin (Suganon®) if appropriate.

3.) Bullous pemphigoid - Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with other DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Evogliptin (Suganon®). If bullous pemphigoid is suspected, Evogliptin (Suganon®) should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Administer with Caution

1) Heart failure: Caution should be exercised for patients with functional class I heart failure based on the New York Heart Association (NYHA) criteria as experience of administration is limited insuch patients. Use of Evogliptin (Suganon®) is not recommended to patients with functional class II-IV based on the NYHA criteria due to the absence of clinical experience in such patients.
2) Renal impairment: It is confirmed that approximately 46.1% of the radioactivity administered bylabeling evogliptin was excreted in urine and approximately 42.8% in feces in adults. This figure includes both the unchanged form and its metabolites. Skice there is a concern that increased blood concentration of the unchanged form may persist in patients with moderate to severe renal impairment and end-stage renal impairment patients undergoing hemodialysis compared to patients with normal renal function, Evogliptin (Suganon®) should be cautiously administered while monitoring the patient's condition. Evogliptin can be administered regardless of the time point of dialysis in end-stage renal impairment patients requiring hemodialysis (Refer to PHAMACOKINETICS: > Characteristics in patients> ii. Renal impairment)
3) Severe hepatic impairment: No study was conducted in patients with severe hepatic impairment. Therefore, caution should be exercised in such patients
4) Acute pancreatitis: There have been reports on acute pancreatitis in patients treated with Evogliptin (Suganon®). Thus, characteristic symptoms of acute pancreatitis such as consistent and severe abdominal pain should be informed to patients. If pancreatitis is suspected after administration of Evogliptin (Suganon®), the administration of Evogliptin (Suganon®) should be discontinued and Evogliptin (Suganon®) should not be re-administered. Caution should be exercised in patients with a medical history of pancreatitis.

PREGNANCY AND LACTATION:
Use in Pregnant Women
No comparative study result is available in pregnant women. Results of animal studies showed that evogliptin was detected in the blood stream of fetus across the placenta up to 61.7% in pregnant rats and 14.1% in pregnant rabbits 2 hours after administration. Therefore, use in pregnant women is not recommended.

Use in Nursing Mothers
It is not evaluated whether Evogliptin (Suganon®) is excreted in human milk. Since animal studies confirmed that evogliptin is secreted in the milk, Evogliptin (Suganon®) should not be used in nursing mothers.

Use in Pediatrics
Safety and efficacy in pediatrics have not been established.

Use in the Elderly
There were 119 elderly patients (22.6%) aged 65 years or older out of a total of 527 patients in the phase II and III clinical studies of Evogliptin (Suganon®). The administration in elderly patients has not been fully investigated. Since the elderly generally have decreased physiological functions such as hepatic and renal functions, caution needs to be exercised during administration while monitoring the patient's condition.

INTERACTIONS:

1) Evogliptin is mainly metabolized by CYP3A4. In in vitro studies, evogliptin was not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzymes or an inducer of CYP1A2, 2B6, and 3A4 enzymes. Thus, evogliptin is unlikely to cause interactions with other drugs acting as a substrate of such enzymes. Although evogliptin was proved to be a p-glycoprotein (P-gp) substrate and weak BCRP substrate based on in vitro studies, it did not inhibit transport mediated by these transporters. In addition, evogliptin was not a substrate of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 and did not inhibit them. Therefore, evogliptin is unlikely to cause interactions with drugs that act as a substrate of such transporters in the clinical dose.
2) Interaction of evogliptin with other drugs
Metformin: Multiple administration of evogliptin 5 mg and twice daily metformin 1,000 mg (a substrate of OCT1 and OCT2) until steady state was reached did not show clinically meaningful change in the pharmacokinetics of evogliptin or metformin.
Clarithromycin: Multiple administration of a potent CYP3A4 inhibitor, clarithromycin 1,000 mg/day, until steady state was reached and single administration of evogliptin 5 mg showed increased Cmax of evogliptin by 2.1 times and its AUC by 2.0 times. Caution needs to be exercised as pharmacokinetic exposure of evogliptin may increase with concomitant administration of CYP3A4 inhibitors.
Rifampicin: Multiple administration of a potent CYP3A4 inducer, rifampicin 600 mg/day, until steady state was reached and single administration of evogliptin 5 mg showed no significantchange in Cmax of evogliptin but showed a decrease in AUC by 63%.
Pioglitazone: Multiple administration of evogliptin 5 mg and pioglitazone 30 mg (a substrate of CYP2C8 and CYP34) did not show clinically meaningful change in the pharmacokinetics of evogliptin or pioglitazone.
Glimepiride: Multiple administration of evogliptin 5 mg and glimepiride 4 mg (a substrate of CYP2C9) did not show clinically meaningful change in the pharmacokinetics of evogliptin or glimepiride.
Dapagliflozin: Multiple administration of evogliptin 5 mg and dapagliflozin 10 mg (a substrate of UGT1A9) did not show clinically meaningful change in the pharmacokinetics of evogliptin or dapagliflozin.
Empagliflozin: Multiple administration of evogliptin 5 mg and empagliflozin 25 mg (a substrate of UGT2B7, UGT1A3, UGT1A8 and UGT1A9) did not show clinically meaningful change in the pharmacokinetics of evogliptin or empagliflozin.

ADVERSE DRUG REACTIONS:
Monotherapy
In the 12-week placebo-controlled monotherapy study using 2.5 mg, 5 mg, or 10 mg of Evogliptin (Suganon®) or placebo once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 1.

Table 1. Adverse events reported in 3% or more patients in the 12-week placebo-controlled monotherapy study (regardless of investigator's causality assessment).

Adverse event	Evogliptin 2.5 mg N= 39	Evogliptin 5mg N= 44	Evogliptin 10mg N = 38	Placebo N = 36
Gastritis	2 (5.1%)	1 (2.3%)	0 (0.0%)	0 (0.0%)
Periodontitis	0 (0.0%)	0 (0.0%)	2(5.3%)	0 (0.0%)
Nasopharyngitis	1 (2.6%)	4 (9.1%)	1 (2.6%)	1 (2.8%)
Erectile dysfunction	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)

In the 24-week placebo-controlled monotherapy study using 5 mg of Evogliptin (Suganon®) or placebo once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 2.

Table 2. Adverse events reported in 3% or more patients in the 24-week placebo-controlled monotherapy study (regardless of investigator's causality assessment)

Adverse event	Evogliptin 5mg N = 78	Placebo N = 80
Dyspepsia	0 (0.0%)	3 (3.8%)
Nasopharyngitis	5 (6.4%)	5 (6.3%)
Arthralgia	3 (3.8%)	0 (0.0%)

In patients administering Evogliptin (Suganon®) 5 mg once daily as monotherapy for 52 weeks, the adverse events that occurred during the extension period (last 28 weeks) regardless of causality with increased frequency by 1% or higher compared to those of the 24-week study were toothache (3.1% vs. 1.3%) and contact dermatitis (3.1% vs. 1.3%). Compared to the 24-week study, there was no newly reported adverse event that occurred in two or more patients (3.1%).

Combination therapy
In the 24-week active-drug-controlled combination therapy study with stable doses of metformin and either Evogliptin (Suganon®) 5 mg or sitagliptin 100 mg once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 3.

Table 3. Adverse events reported in 3% or more patients in the 24-week active-controlled combination therapy study (regardless of investigator's causality assessment)

Adverse event	Evogliptin 5 mg N = 111	Evogliptin 5mg N = 44
Dyspepsia	5 (4.5%)	3 (2.8%)
Diarrhoea	4 (3.6%)	1 (0.9%)
Nasopharyngitis	8 (7.2%)	9 (8.3%)
Pruritus	4 (3.6%)	1 (0.9%)

In the 52-week study using Evogliptin (Suganon®) 5 mg once daily combined with metformin, the adverse events that occurred during the extension period (last 28 weeks) regardless of causality with increased frequency by 1% or higher compared to those of the 24-week study were gastritis (2.2% vs. 0.9%) and upper respiratory tract infection (4.3% vs. 2.7%). Compared to the 24-week study, sciatica (2.2%) was a newly reported adverse event that occurred in two or more patients (2.2%).

In the clinical trial in which Evogliptin (Suganon®) 5 mg or a placebo was additionally administered once daily for 52 weeks in patients with type 2 diabetes who have inadequate glycemic control with the stable doses of metformin and dapagliflozin combination therapy, the adverse events reported with a frequency of 1% or higher are listed in Table 4.

Table 4. Adverse events reported in 1% or more patients in the metformin and dapagliflozin combination therapy study (regardless of investigator's causality assessment)

Adverse event	Evogliptin 5mg N=141	Placebo N=141
Gastrointestinal disorders		
Constipation	3(2.13%)	1(0.71%)
Chronic gastritis	3(2.13%)	0(0.00%)
Large intestine polyp	3(2.13%)	0(0.00%)
Gastric ulcer	2(1.42%)	1(0.71%)
Gastrooesophageal reflux disease	2(1.42%)	0(0.00%)
Haemorrhoids	2(1.42%)	0(0.00%)
Dyspepsia	1(0.71%)	2(1.42%)
Infections and infestations		
Vaginal infection	3(2.13%)	0(0.00%)
Herpes zoster	2(1.42%)	1(0.71%)
Cystitis	2(1.42%)	0(0.00%)
Musculoskeletal and connective tissue disorders		
Arthralgia	2(1.42%)	3(2.13%)
Myalgia	2(1.42%)	1(0.71%)
Rotator cuff syndrome	2(1.42%)	2(1.42%)
Intervertebral disc disorder	0(0.00%)	2(1.42%)
Eye disorders		
Diabetic retinopathy	0(0.00%)	2(1.42%)
Injury, poisoning and procedural complications		
Ligament sprain	2(1.42%)	1(0.71%)
Foot fracture	0(0.00%)	2(1.42%)
Nervous system disorders		
Dizziness	2(1.42%)	1(0.71%)
Headache	1(0.71%)	2(1.42%)
Reproductive system and breast disorders		
Breast pain	0(0.00%)	2(1.42%)
Pruritus	0(0.00%)	2(1.42%)
Ear and labyrinth disorders		
Deafness neurosensory	2(1.42%)	0(0.00%)
Vascular disorders		
Hypertension	1(0.71%)	2(1.42%)

Hypoglycemia
In the 24-week monotherapy and combination therapy study with evogliptin 5 mg, hypoglycemia was each reported in one patient (monotherapy 1.3%, combination therapy 0.9%). All reported hypoglycemia cases were mild in severity and resolved without any action taken.

In the clinical trial in which Evogliptin (Suganon®) 5 mg or a placebo was additionally administered once daily for 52 weeks in patients with type 2 diabetes who have inadequate glycemic control with the stable doses of metformin and dapagliflozin combination therapy, hypoglycemia was each reported in one patient (evogliptin 5 mg 0.71%, placebo 0.71%). All were asymptomatic hypoglycemia, resolved during the study without any action taken and the causality was related.

Vital signs
No clinically significant change in vital signs was observed in patients treated with Evogliptin (Suganon®).

Bullous pemphigoid
There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking other DPP-4 inhibitors.

*Post-marketing surveillance result for re-examination in Korea
In the post-marketing surveillance in 3,445 patients for 6 years for re-examination in Korea, the incidence of adverse events, regardless of causality, was 8.59% (296/3,445 patients, 355 cases in total). Of these events, both serious adverse drug reactions and unexpected adverse drug reactions, which the causal relationship with Evogliptin (Suganon®) could not be excluded, are listed in the following table, in the order of frequency.

Frequency	SOC	Serious Adverse Drug Reaction 0.09% (3/3,445 patients, 3 cases)	Unexpected Adverse Drug Reaction 0.61% (21/3,445 patients, 24 cases)
Uncommon, Infrequent (≥0.1% and < 1%	Gastrointestina 1 disorders	-	Nausea
Rare (≥0.01% and <0.1%)	Nervous system disorders	-	Headache, Dizziness, Parosmia
	Gastrointestina 1 disorders	Dyspepsia	Constipation
	Musculoskelet al and connective tissue disorders	-	Myalgia
	Skin and subcutaneous tissue disorders	-	Urticaria, Rash
	Investigations	-	Liver function test increased, Weight decreased
	Immune system disorders	-	Drug hypersensitivity
	Metabolism and nutrition disorders	Hyperglycaemic hyperosmolar nonketotic syndrome	Hyperglycaemic hyperosmolar nonketotic syndrome
	Psychiatric disorders	-	Insomnia
	Cardiac disorders	Palpitations	Palpitations
	Respiratory, thoracic and mediastinal disorders	-	Epistaxis
	Renal and urinary disorders	-	Renal impairment
	Reproductive system and breast disorders	-	Sexual dysfunction

OVERDOSE AND TREATMENT:
In clinical trials of Evogliptin (Suganon®), single dose of Evogliptin (Suganon®) up to 60 mg daily was administered in healthy adults. In case of an overdose, perform symptomatic therapy (e.g., remove unabsorbed substance from the gastrointestinal tract, conduct clinical monitoring including electrocardiogram), and perform supportive therapy depending on the patient's condition.

STORAGE CONDITIONS:
Store at temperatures not exceeding 30°C.

AVAILABILITY:
Alu/OPA/PVC blister film/Alu blister pack x 10's (Box of 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL:
Keep out of reach of children. As keeping this drug in other containers may result in an accident caused by misuse or in decreased quality of the drug, store in the original container.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING:
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Patients should seek medical attention immediately at first sign of any adverse drug reaction.

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MANUFACTURED BY:
DONG-A ST
Bldg. #2, 6, 7, 8, 45,
Jisikgiban-ro Yeonsu-gu,
Incheon, Republic of Korea

IMPORTED AND EXCLUSIVELY DISTRIBUTED BY:
MPP® METRO PHARMA PHILIPPINES, INC.
24F Unit K, The Glaston Tower, Ortigas East, E. Rodriguez Jr. Ave.,
Ugong, Pasig City, Metro Manila