ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ENVLO 0.3 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.3 mg Enavogliflozin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pale-orange, biconvex, triangular, film-coated tablet with “E” on one side and “03” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENVLO 0.3 mg film-coated tablets is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, when metformin, along with diet and exercise, does not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology
The recommended dose of Enavogliflozin is 0.3 mg once daily, for add-on combination therapy with metformin.

Method of administration
The tablets can be taken with or without food, swallowed whole with water.

Special populations
Patients with Renal Impairment
Efficacy of enavogliflozin depends on renal function. Safety and Efficacy have not been established in patients with moderate and severe renal impairment. Patients with an eGFR less than 60 mL/min/1.73 m ^{2} should not initiate treatment with enavogliflozin. Enavogliflozin should be discontinued if eGFR is consistently less than 60 mL/min/1.73 m^2.
No dose adjustment is needed in patients with mild renal impairment.

4.3 Contraindications

It should not be used in these patients
1) History of serious hypersensitivity reaction to Enavogliflozin or any of its components.
2) Type 1 diabetes or diabetic ketoacidosis.
3) eGFR of less than 30 mL/min/1.73m^2, end-stage renal disease (ESRD) or dialysis.
4) Moderate and severe hepatic impairment.

4.4 Special warnings and precautions for use

General
Envlo should not be used in patients with type 1 diabetes mellitus or for the treatment diabetic ketoacidosis.

It should be used with caution in these patients

1) Administration in patients with decreased volume of body fluid and impaired renal function
Enavogliflozin may cause symptomatic hypotension or hypovolemia in the blood vessels that may manifest as rapid and transient changes in creatinine. Acute renal impairment has been reported in patients treated with other SGLT2 inhibitors, some requiring hospitalization and dialysis. The risk of hypovolemia or hypotension may increase in patients with renal dysfunction (eGFR less than 60 mL/min/1.73 m^2), the elderly, or those using loop diuretics. Patients with those characteristics should be evaluated for body fluid status and renal function before starting administration of enavogliflozin. After starting administration, hypotensive symptoms and signs and renal function should be monitored.
Based on its mechanism of action, efficacy of enavogliflozin depends on renal function.
Serum creatinine may increase or eGFR may be decreased with this treatment. Renal function should be evaluated regularly and patients with renal impairment should be monitored thoroughly during treatment. Assessment of renal function is recommended as follows:

- Prior to enavogliflozin with metformin initiation and thereafter periodically
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function
- In patients with eGFR of less than 60 mL/min/1.73m^2, more frequently.

2) Heart failure
Since experience with NYHA class I-II is limited, it should be used with caution in these patients. Enavogliflozin in NYHA class III-IV is not recommended as there is no experience with this treatment.

3) Patients with Hepatic Impairment
Since experience in patients with mild hepatic impairment is limited, it should be used with caution in these patients.

4) The following patients or conditions: May cause hypoglycemia

- Hypopituitarism or adrenal insufficiency
- Malnutrition, starvation, irregular eating habits, insufficient of food intake or hyposthenia
- Patients who muscle exercise vigorously
- Excessive alcohol intake

5) Ketoacidosis
Reports of serious, life-threatening ketoacidosis requiring rapid hospitalization have been identified in clinical trials and post-marketing surveillance in patients taking other SGLT2 inhibitors. Since ketoacidosis can occur with enavogliflozin even if the blood sugar level is lower than 250 mg/dL (14 mmol/L), if there are signs and symptoms of severe metabolic acidosis in patients taking enavogliflozin, a ketone testing should be performed regardless of blood glucose level. If ketoacidosis is suspected, administration of enavogliflozin should be discontinued immediately, with evaluation of the patient's condition and prompt appropriate measures. Treatment of ketoacidosis may require the supplementation of insulin, body fluid and carbohydrate.
Signs and symptoms of ketoacidosis are consistent with dehydration and severe metabolic acidosis, including nausea, vomiting, epigastric pain, malaise and dyspnea. In some reports, decreased insulin dose, acute febrile illness, caloric restriction due to illness or surgery, pancreatic disorders causing insulin deficiency (such as type 1 diabetes mellitus, pancreatitis or a history of pancreatic surgery), and

alcohol abuse has been identified as a factor inducing ketoacidosis. Before starting treatment with enavogliflozin, the patient's history and factors that may cause ketoacidosis, including reduced insulin secretion, caloric intake restriction, and alcohol abuse, should be considered. Patients treated with enavogliflozin should be monitored for the occurrence of ketoacidosis, and if clinical conditions likely to induce ketoacidosis (e.g., prolonged fasting due to acute illness and surgery) occur, treatment with enavogliflozin should be temporarily discontinued.

6) Urinary Tract Infections and Genital Infections

Enavogliflozin may increase the risk of or worsen urinary tract and genital infections and should be monitored and treated appropriately. In clinical trials with other SGLT2 inhibitors, urinary tract infections were reported more frequently than in the placebo group, and patients with a history of genital fungal infections and uncircumcised men were more likely to develop genital fungal infections. [Refer to 4.8 Undesirable effects 3) and 4.4 General Caution 2), 5)]

7) Patients at risk of dehydration (very insufficient blood sugar control, the elderly, taking concomitant diuretics, etc.)

Dehydration may occur due to the diuretic action of enavogliflozin.

8) General Caution

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

Diuretic action according to the mechanism of action of SGLT2 inhibitors may cause polyuria and frequent urination, and osmotic diuresis accompanying glucoseuria may cause a slight drop in blood pressure. Patients receiving antihypertensive therapy with a history of hypotension, or patients at risk of drug-induced blood pressure reduction, such as the elderly, should be cautioned and instructed on adequate hydration. If abnormalities such as dehydration and decreased blood pressure occur, appropriate measures such as discontinuation of drug administration and replacement of body fluids should be taken. In particular, patients with a tendency to decreased body fluid proportion (the elderly, patients concomitantly taking diuretics, etc.) should be cautious in relation to dehydration, diabetic ketoacidosis, hyperosmotic hyperglycemic syndrome, and thromboembolism including cerebral infarction.

Genital Infections

Enavogliflozin increases the risk of genital infections (Including mycotic). Patients with a history of genital infections (including mycotic) are more likely to develop genital infections (including mycotic). They should be properly observed and treated.

Increased Urine Output

SGLT2 inhibitors, such as enavogliflozin, could theoretically aggravate the disease state due to increased urine output in patients with underlying bladder disease that may affect urination. Therefore, caution is required when prescribing SGLT2 inhibitors such as enavogliflozin to these patients. In patients presenting with symptoms of dysuria, anuria, hypouresis or urinary retention, treatment of these symptoms should be prioritized and treatment with other medications should be considered.

Ketoacidosis

Even if blood sugar is sufficiently controlled by the urine glucose excretion, which is a mechanism of action of enavogliflozin, ketosis may occur due to increased fatty acid metabolism.
Ketoacidosis can occur without a significant increase in blood glucose, especially in patients with reduced insulin secretion, dose reduction or discontinuation of insulin preparations, excessive restriction of carbohydrate intake, poor dietary intake, infection, and/or dehydration. Patients should be provided with information about symptoms of ketoacidosis (such as nausea and vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnoea and/or decreased consciousness). If these symptoms

are observed, the patient should be instructed to visit a medical institution immediately.

Urinary sepsis and pyelonephritis
Serious urinary tract infections, including urosepsis and pyelonephritis, have been reported post-marketing in patients using other SGLT2 inhibitors. SGLT2 inhibitor therapy increases the risk of urinary tract infections. If necessary, examine the patient for signs and symptoms of urinary tract infection and treat promptly.

Urine Laboratory Evaluation
Patients taking enavogliflozin will test positive for glucose in urine due to its mechanism of action.

Hypoglycemia
Hypoglycemic symptoms may occur. It should be cautious when engaging in activities such as working at heights or driving a car.

Weight Loss
Weight loss has been reported as a result of treatment with enavogliflozin. Attention is required for excessive weight loss.

Lower limb amputation
In long-term clinical studies of other SGLT2 inhibitors, an increase in lower limb amputations (mainly toes) has been observed. It has not been confirmed whether this case applies to all the SGLT2 inhibitors. As with all diabetics, it is important to consult with the patient about routine preventive foot care.

Gangrene of the perineum (Fournier's gangrene)
In post-marketing surveillance of diabetic patients taking SGLT2 inhibitors, a rare but life-threatening severe perineal gangrene requiring rapid surgical intervention was reported. Perineal gangrene has been reported in both men and women, resulting in hospitalizations, multiple surgeries, and deaths. Perineal gangrene should be checked if pain, soreness, erythema, or swelling around the genital or perineal area, along with fever and discomfort occurs in patients receiving enavogliflozin. If perineal gangrene is suspected, broad-spectrum antibiotic treatment should be initiated immediately and, if necessary, surgical resection should be performed. Administration of enavogliflozin should be discontinued and appropriate alternative treatment for blood glucose control should be implemented while blood glucose levels are closely monitored.

Pediatric Administration
The clinical safety and efficacy of enavogliflozin in children and adolescents have not been established.

Administration to the elderly
- The elderly are generally in a state of reduced physiological function. Enavogliflozin should be administered with caution while closely monitoring the patient’s condition.
- Elderly patients are more likely to have renal impairment or are taking antihypertensive drugs that can alter renal function, such as angiotensin-converting enzyme inhibitors (ACE-I) and Angiotensin II Type 1 Receptor Blockers. In the case of the elderly, dehydration symptoms (including thirst) may be recognized late, so caution should be exercised. The elderly may be at an increased risk of volume depletion and more likely to be on diuretics.
- Due to limited experience in patients over 80 years of age, initiation of enavogliflozin with metformin is not recommended.

Administration to patients with renal impairment
In a phase 1 clinical trial conducted in type 2 diabetic patients with different renal function, the efficacy was dependent on renal function when 0.5 mg was administered. No dose adjustment is necessary in patients with mild renal impairment, and treatment with enavogliflozin should not be initiated in patients

with moderate to severe renal impairment with a glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 as safety and efficacy have not been established. If the glomerular filtration rate (eGFR) is consistently less than 60 mL/min/1.73 m^2, the drug should be discontinued.

Administration to patients with hepatic impairment
Experience in patients with mild hepatic impairment is limited, so it should be used with caution in these patients. Patients with moderate to severe hepatic impairment have not been studied.

4.5 Interaction with other medicinal products and other forms of interaction

1) Enavogliflozin is mainly metabolized by cytochrome P450 (CYP) 3A4. In-vitro, Enavogliflozin and its active metabolite M1 did not inhibit CYP isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) and UGT isoenzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7). No induction effect was observed for CYP3A4, CYP1A2, and CYP2B6.
In-vitro, enavogliflozin is a substrate for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and P-gp. Enavogliflozin did not inhibit OCT1, OCT2, OAT1, or BCRP transporters.
Active metabolite M1 did not inhibit OAT1, OAT3, OATP1B1, NTCP, P-gp, and BCRP.

2) No clinically significant pharmacokinetic interaction was observed when enavogliflozin was administered in combination with metformin.
① Metformin: When 2 mg of enavogliflozin and 1000 mg of metformin were co-administered, the pharmacokinetic properties of metformin did not change, and the maximum plasma concentration (C_{max}) of enavogliflozin increased by 21%, but the area under the blood concentration-time curve (AUC) did not change.

4.6 Fertility, pregnancy and lactation

1) Pregnancy
There are no adequate and well-controlled clinical trial data in pregnant women. The use of enavogliflozin in pregnant women is not recommended. Once pregnancy is confirmed, the administration of enavogliflozin should be discontinued. Animal study(rat) show that enavogliflozin do not indicate harmful effects with respect to early embryonic development. As a result of embryo-fetal development studies in rats and rabbits, maternal weight gain was decreased, but there was no effect on embryo-fetal development (Transfer to the fetuses has been reported in rat studies.)

2) Breast-feeding
No data in human are available on excretion of enavogliflozin into milk. As available data in rat have shown excretion of enavogliflozin in milk, enavogliflozin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Symptoms of hypoglycemia may occur. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines.

4.8 Undesirable effects

1) Summary of safety profile
To evaluate the safety of enavogliflozin, one phase 1 study for Pharmacokinetics and pharmacodynamics evaluation and one 12-week phase 2 study for dose determination were conducted. In phase 3 study, combination therapy with metformin was conducted for 24-week. A 52-week long-term

administration clinical trial was conducted in a combination therapy with metformin.
A total of 200 patients with type 2 diabetes was included in a combination therapy with metformin Among patients who participated 24-week duration, 99 patients received active control, and 101 patients treated with enavogliflozin.

2) List of adverse reactions
In a phase 3 clinical trial evaluating metformin combination therapy conducted as an active control study, adverse reactions reported in 1% or more in patients treated with the active control drug or enavogliflozin were classified by System Organ Class (SOC) and MedDRA terms and are shown in Table 1.

Table 1. Adverse reactions reported at ≥ 1% in active control combination clinical trials[a]

	Metformin combination[b]		Metformin combination extension[c]	
	Enavogliflozin N=101(%)	Dapagliflozin N=99(%)	Maintenance groups[d] N=82(%)	Switching group[e] N=77(%)
Gastrointestinal disorders				
Dyspepsia	1 (0.99)	2 (2.02)*	0	0
Constipation	0	1 (1.01)	0	0
Gastritis	0	2 (2.02)	1 (1.22)	0
Abdominal pain upper	0	2 (2.02)	0	0
Chronic gastritis	1 (0.99)	0	1 (1.22)	0
Gastrooesophageal reflux disease	0	2 (2.02)	0	1 (1.30)
Mechanical ileus	1 (0.99)	0	1 (1.22)	0
Diverticulum intestinal	0	0	1 (1.22)	0
Vomiting	0	1 (1.01)	0	0
Infections and infestations				
Vaginal infection	0	0	1 (1.22)*	0
Nasopharyngitis	0	0	1 (1.22)	0
Cystitis	1 (0.99)*	1 (1.01)*	0	0
Latent tuberculosis	0	0	0	1 (1.30)
Coronavirus infection	0	0	1 (1.22)	0
Tonsillitis	0	1 (1.01)	0	0
Viral skin infection	0	0	0	1 (1.30)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0.99)	1 (1.01)	0	1 (1.30)
Myalgia	1 (0.99)	1 (1.01)	0	1 (1.30)
Synovial cyst	1 (0.99)	0	1 (1.22)	0
Intervertebral disc disorder	0	0	0	1 (1.30)

Scoliosis	0	0	0	1 (1.30)
Injury, poisoning and procedural complications				
Skin laceration	0	0	0	1 (1.30)
Foot fracture	0	0	1 (1.22)	0
Joint dislocation	0	0	0	1 (1.30)
Tibia fracture	0	0	0	1 (1.30)
Nervous system disorders				
Headache	2 (1.98)	2 (2.02)	0	1 (1.30)
Dizziness	0	1 (1.01)	0	0
Hypoaesthesia	0	0	1 (1.22)	0
Facial paralysis	0	0	0	1 (1.30)
Skin and subcutaneous tissue disorders				
Pruritus	0	2 (2.02)*	0	0
Dermatitis	0	1 (1.01)	0	0
Dermatitis contact	0	1 (1.01)	0	0
Rash	0	1 (1.01)	0	0
Metabolism and nutrition disorders				
Dyslipidaemia	2 (1.98)	0	0	0
Hypoglycaemia	0	1 (1.01)	1 (1.22)	2 (2.60)
Hyperlipidaemia	0	0	1 (1.22)	0
Reproductive system and breast disorders				
Benign prostatic hyperplasia	0	1 (1.01)	0	0
Vulvovaginal pruritus	0	1 (1.01)*	0	0
Renal and urinary disorders				
Pollakiuria	0	1 (1.01)*	0	0
Nephrolithiasis	0	1 (1.01)	0	0
Renal cyst	0	1 (1.01)	0	0
Hepatobiliary disorders				
Cholelithiasis	0	0	1 (1.22)	0
Hepatic steatosis	0	2 (2.02)	0	0
Cardiac disorders				
Angina unstable	0	0	1 (1.22)	0
General disorders and administration site conditions				
Chest pain	0	0	0	1 (1.30)
Neoplasms benign, malignant and unspecified(incl cysts and polyps)				
Colon adenoma	0	0	1 (1.22)	0
Gastrointestinal submucosal tumour				

Neuroma	0	0	1 (1.22)	0
Prostate Cancer	0	1 (1.01)	0	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	0	1 (1.01)	0	0
Hyperventilation	0	1 (1.01)	0	
Blood and lymphatic system disorders				
Leukocytosis	0	1 (1.01)	0	0
Vascular disorders				
Varicose vein	0	0	1 (1.22)	0
Psychiatric disorders				
Insomnia	0	0	1 (1.22)	0

[a] Drug adverse reactions that cannot be excluded from the causal relationship with enavogliflozin were marked with (adverse reaction name*). The incidence of adverse reactions in all groups for adverse reactions reported at 1% or more in any one group was described.
[b] These is the analysis result of phase 3 clinical trial of metformin combination therapy, and the trial was conducted as active control clinical trials for 24 weeks.
[c] Adverse reactions were reported in patients who took one or more doses of enavogliflozin for an extended period (25 to 52 weeks) after enrolling in an extension clinical trial of metformin combination therapy.
[d] Maintenance groups: 0-24 weeks enavogliflozin 0.3 mg, 25-52 weeks enavogliflozin 0.3 mg administration (metformin administration continued)
[e] Switching group: 0-24 weeks dapagliflozin 10 mg, 25-52 weeks enavogliflozin 0.3 mg administration (metformin administration continued)

In the phase 3 clinical trial of metformin combination therapy conducted for 24 weeks, the adverse reactions reported in less than 1% in the drug-administered group are listed according to System Organ Class (SOC) as follows. Adverse drug reactions that cannot be excluded from a causal relationship with enavogliflozin are indicated with (adverse reaction name*).

- Infections and parasitic infections: cystitis*, COVID-19, periodontitis, sinusitis
- Immune system disorders: food allergy
- Endocrine disorders: hypothyroidism, thyroid cyst, thyroid mass
- EYE disorders: cataract
- Vascular disorders: arteriosclerosis, hypertension
- Gastrointestinal disorders: dyspepsia, anal fissure, chronic gastritis, large intestine polyp, mechanical ileus, nausea
- Hepatobiliary disorders: hepatic function abnormal
- Skin and subcutaneous tissue disorders: urticaria
- Musculoskeletal and connective tissue disorders: arthralgia, myalgia, back pain, neck pain, rotator cuff syndrome, synovial cyst, temporomandibular joint syndrome
- Renal and urinary disorders: haematuria
- Reproductive system and breast disorders: sexual dysfunction
- Injury, poisoning and procedural complications: contusion, concussion

3) Description of selected adverse reactions
Hypoglycaemia
During the extended period (25 to 52 weeks) of metformin combination therapy out of the clinical trial, hypoglycemia was reported in 3 patients (1.89%) in the enavogliflozin group.

Urinary tract and genital infections
There were no adverse reactions reported as urinary tract infections in the enavogliflozin-treated group in the clinical trial. In the phase 3 clinical trial of metformin combination therapy, cystitis was

reported in 1 patient (0.99%) and during the extended period (25 to 52 weeks) vaginal infection was reported in 1 patient (0.63%) in enavogliflozin- treated group.

Frequent urination and Polyuria
There were no adverse reactions reported as pollakiuria in the enavogliflozin-treated group in the clinical trial.

4) Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional	***PT Daewoong Pharmaceutical Indonesia***
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif *Badan Pengawas Obat dan Makanan* *Email: pv-center@pom.go.id* *Website: https://e-meso.pom.go.id/ADR*	*WeWork Revenue Tower 20th Floor SCBD, Lot 13 District 8, Jl. Jenderal Sudirman Kav. 52-53 RT. 5 RW.3, Senayan, 12190* *24-hour Pharmacovigilance Unit* *Phone: +62 889-7580-0212* *Email:* safety_dwi@daewoong.co.kr *Website:* https://daewoongpharm.id/

4.9 Overdose

No toxicity was observed in single oral administration of up to 5 mg (17 times the recommended human dose) and repeated oral administration of up to 2 mg (7 times the recommended human dose) in healthy adults. Subjects had detectable urinary glucose excretion during the dosing period (up to 7 days after the end of dosing), and no reports of dehydration, hypotension, hypoglycemia, or electrolyte imbalance. In case of overdose, appropriate symptomatic treatment should be administered according to the patient's clinical condition. The elimination of enavogliflozin on hemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
ATC Code: A10BK09
Enavogliflozin is a selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is highly expressed in the kidney. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2 and inducing excretion of glucose, enavogliflozin drops blood glucose level. Enavogliflozin elevates hematocrit and losses weight. In *in vitro* studies, compared with SGLT-1, the major cotransporter involved in glucose reabsorption in the gastrointestinal tract, enavogliflozin selectively inhibited human SGLT2. The inhibitory concentration (IC50) of SGLT-1 was 436 nmol/L and SGLT2 was 0.43 nmol/L.

Clinical efficacy and safety
1) Add-on Combination therapy with metformin
Clinical trial of metformin combination therapy
In a clinical study in which 0.3 mg of enavogliflozin or 10 mg of dapagliflozin was administered for 24 weeks to type 2 diabetic patients whose blood sugar was not adequately controlled even with metformin, compared to the dapagliflozin-treated group (dapagliflozin and metformin), the change in HbA1c in the 0.3 mg-administered group (enavogliflozin and metformin) was statistically non-inferior.

During the 52-week extended period of this study, there was a significant decrease in both the maintenance group[1)] administered with 0.3 mg of enavogliflozin and the switching group[2)] administered

10 mg of dapagliflozin for 24 weeks, followed by with 0.3 mg of enavogliflozin for 28 weeks.

Table 2. Efficacy results at 24 week compared to the reference drug when enavogliflozin was co-administered with metformin.

HbA1c (%)	metformin + enavogliflozin 0.3 mg	metformin + dapagliflozin 10 mg
The primary endpoint: HbA1c (%)		
Number of subjects[a]	95	90
HbA1c (%) baseline mean (SD)	7.75(0.82)	7.68(0.73)
Difference from baseline after 24 weeks (LS Mean (SE))[b]	-0.80(0.06)	-0.75(0.06)
Difference from metformin + dapagliflozin [95% CI][a]	-0.04 [-0.21, 0.12][c]	
Percent of patients achieving HbA1c <7% (%)	61.1%	62.2%
Percent of patients with achieving greater than 0.5% reduction in HbA1c or achieving HbA1c <7% (%)	78.9%	75.6%

a: Per-Protocol Set (PPS)

b: ANCOVA (analysis of covariance) (model includes stratification factor and baseline HbA1c as covariates and treatment group as a factor)

c: Non-inferior if the upper bound of the 95% confidence interval is less than 0.35%

Table 3. Efficacy results at 52 week compared to reference drug when enavogliflozin was co-administered with metformin.

HbA1c (%)	maintenance group[1)]	switching group[2)]
The primary endpoint: HbA1c (%)		
Number of subjects[a]	81	76
HbA1c (%) baseline mean (SD)	7.72(0.85)	7.72(0.76)
Difference from baseline after 52 weeks (LS Mean (SE))[b]	-0.87(0.08)	-0.81(0.08)
Percent of patients achieving HbA1c <7% (%)	67.9%	63.2%
Percent of patients with achieving greater than 0.5% reduction in HbA1c or achieving HbA1c <7% (%)	81.5%	76.3%

[1)] Maintenance groups: 0-24 weeks enavogliflozin 0.3 mg, 25-52 weeks enavogliflozin 0.3 mg administration (metformin administration continued)

[2)] Switching group: 0-24 weeks dapagliflozin 10 mg, 25-52 weeks enavogliflozin 0.3 mg administration (metformin administration continued)

a: Full Analysis Set (FAS)

b: LOCF: last observation carried forward.

c: ANCOVA (analysis of covariance) (model includes stratification factor and baseline HbA1c as covariates and treatment group as a factor)

5.2 Pharmacokinetic properties

1)Absorption

Enavogliflozin is rapidly absorbed after oral administration. When enavogliflozin was single administered to healthy adults on a fasting state, C_{max} was reached within 1.0 to 1.5 hours, and C_{max} and AUC increased proportionally to the dose. Steady state was reached after 4 to 7 days when enavogliflozin was administered once a day for 15 days. When 0.3 mg of enavogliflozin was administered once a day for 15 days, $C_{max,ss}$ and AUC_t were 6.43 μg/L and 42.12 μg*h/L, respectively, in the steady state. When administered with a high-fat diet, the C_{max} of enavogliflozin was reduced by 57% compared to the fasting state, and the AUC was unchanged.

2)Distribution

The plasma protein binding ratio of enavogliflozin was 99.0% to 99.9%, and was independent of the concentration of enavogliflozin in the evaluated range (100 to 1000 ng/mL) (*in vitro*).

3)Metabolism
The major route of elimination is hepatic metabolism. The metabolic pathways of enavogliflozin were hydroxylation by CYP3A4 and glucuronidation by UGT1A4, UGT1A9, and UGT2B7, and it was confirmed that M1 and M2 were produced by hydroxylation (*in vitro* test). When 0.1 to 2 mg of enavogliflozin was administered to healthy adults for 15 days, the main circulating plasma was the parent of enavogliflozin and its active metabolite M1 (20% to 25% of the mother).
Enavogliflozin did not inhibit CYP and UGT isoenzymes and did not induce CYP1A2, 2B6, and 3A4 metabolizing enzymes (*in vitro* test). Therefore, no drug interactions involving the major CYP450 and UGT isozymes are expected when enavogliflozin and substrate drugs of these enzymes are co-administered.

4)Excretion
When enavogliflozin[^{14}C] was orally administered to rats, urinary and fecal excretion rates were 3.9% and 97.2% (total 101.4%), respectively, for 96 hours after administration. Through this, it was confirmed that almost all of the radioactivity administered was excreted in urine or feces. Therefore, biliary excretion is expected to be the main route of excretion after oral administration of enavogliflozin. In healthy adults, the elimination half-life ($t_{½}$) of enavogliflozin was about 13.71 to 27.88 hours when administered as a single oral dose in the range of 0.2 to 5 mg, and the urinary excretion rate of unchanged drug was less than 1.76%. Therefore, the main route of excretion after oral administration of enavogliflozin does not appear to be renal.

5)Special Group
Renal Impairment
When 0.5 mg of enavogliflozin was administered on fasting state to 22 type 2 diabetic patients with normal or reduced renal function, the Geometric Mean Ratios(GMR)(90% CI) of C_{max} and AUC_t in patients with mild renal impairment (eGFR ≥60 to <90 mL/min/1.73m^2; 7 patients) compared to patients with normal renal function (eGFR ≥90 mL/min/1.73m^2; 6 patients) were 0.8801 (0.7301 to 1.0610) and 0.8456 (0.6638 to 1.0772), respectively. In patients with moderate renal impairment (eGFR ≥30 ~ <60 mL/min/1.73m^2; 4 patients), they were 0.7797 (0.6105 ~ 0.9959) and 0.9535 (0.6945 ~1.3091), respectively. In patients with severe renal impairment (eGFR ≥15 to <30 mL/min/1.73 m^2; 5 patients), the values were 0.7405 (0.6005 to 0.9131) and 0.8053 (0.6138 to 1.0563), respectively. Mean urinary glucose excretion for 24 hours after single dose of enavogliflozin was 92.25g, 78.42g, 32.69g, and 4.33g in patients with normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment, respectively.

Hepatic Impairment
No separate clinical trials were conducted in type 2 diabetic patients with reduced liver function. Patients with moderate to severe hepatic impairment were not included in the clinical trial of enavogliflozin.

Elderly
Of the 101 patients who took enavogliflozin at least once in the clinical trial of enavogliflozin, 68(67.3%) were under the age of 65, 33(32.7%) were over the age of 65, and 8(7.9%) were over the age of 75. As a result of subgroup analysis for the clinical trial, there was no significant difference in HbA1c change between those under 65 years of age and those over 65 years of age.

5.3 Preclinical safety data

Mutagenicity
Enavogliflozin did not cause mutagenicity in an Ames mutagenicity assay, *in vitro* mammalian chromosomal aberration test, and *in vivo* micronucleus assay in rats regardless of the presence or absence of metabolic activity.
The active metabolite M1 did not cause mutagenicity or mutagenicity in the reverse mutation (Ames)

test regardless of metabolic activity.

Reproductive Toxicity

1) Fertility

Fertility and early embryonic development studies were conducted by orally administering enavogliflozin to male and female rats at doses of 3, 10, and 30 mg/kg/day.
The NOAEL for male and female fertility and early embryo development was 30 mg/kg/day. The exposure at NOAEL is 1,567 times higher for males and 1,745 times higher for females than the recommended human dose (0.3 mg/day) of enavogliflozin.

2) Teratogenicity

In the reproductive toxicity test conducted in rats and rabbits, the NOAEL of the mother and fetus were 10 mg/kg/day and 30 mg/kg/day. These are doses corresponding to 776 and 197 times the recommended human dose exposure of enavogliflozin, respectively.

3) Pre- and Post-Natal Development

When administered orally at doses of 3, 10, and 30 mg/kg/day for prenatal and postnatal development and maternal function in rats, at the high dose of 30 mg/kg/day, weight gain and loss were observed, but functional growth and reproductive performance of the fetus were not affected. The NOAEL for maternal reproductive function and offspring is both 10 mg/kg/day, which is 776 times higher than the recommended human exposure (0.3 mg/day).

Carcinogenicity

Carcinogenicity study of enavogliflozin was conducted in Sprague-Dawley rats and CD-1 mice. As a result of a carcinogenicity test conducted for 2 years at doses of 1, 3, and 10 mg/kg/day in male and female rats, no tumors were observed in female rats. At a dose of 10 mg/kg/day in male rats, an increased incidence of benign adrenal medullary pheochromocytoma was confirmed as a drug-related tumor. However, this is considered to be an increase in species-specific pheochromocytoma limited to rats. A dose of 10 mg/kg/day in rats has an exposure equivalent to more than 100 times the human exposure seen at the recommended human dose of 0.3 mg of enavogliflozin when compared on the basis of AUC.
A carcinogenicity study was conducted for 2 years in male and female mice at doses of 3, 6, and 12 mg/kg/day. No tumors were observed up to a dose of 12 mg/kg/day, which was more than 100 times higher than the recommended human dose of 0.3 mg of enavogliflozin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Colloidal silicon dioxide
Hydroxypropylcellulose
Magnesium Stearate
Croscarmellose sodium

Film coating
Hypromellose 2910
Titanium dioxide
Polyethylene glycol 400

Iron oxide yellow
Iron oxide red

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

1) Keep out of reach of children.
2) Be aware that changing to another container can cause an accident or is undesirable in terms of quality maintenance.

6.5 Nature and contents of container

Aluminium-aluminium blister, each blister contains 10 tablets (30 tablets /box)

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF MANUFACTURER
Daewoong Pharmaceutical Co., Ltd.
Cheongju-si, Republic of Korea

8. MARKETING AUTHORISATION HOLDER
PT Daewoong Pharmaceutical Indonesia, Cikarang, Indonesia
Phone: +62 21 3972 1100, Website: https://daewoongpharm.id/

9. MARKETING AUTHORISATION NUMBER(S)
ENVLO, 0.3 mg Film-coated Tablets, Box of 3 blisters @ 10 film-coated tablets
Reg. No.

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
December 22, 2025

11. DATE OF REVISION OF THE TEXT
December 23, 2025

HARUS DENGAN RESEP DOKTER

Informasi Produk untuk Pasien

ENVLO

Enavogliflozin 0,3 mg

Tablet Salut Selaput

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi hal-hal penting untuk Anda

- Simpanlah leaflet ini. Anda mungkin perlu membacanya di kemudian hari
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakanlah dokter, apoteker, atau perawat Anda
- Obat ini telah diresepkan khusus untuk Anda. Dilarang memberikan obat ini untuk orang lain karena hal ini dapat membahayakan mereka, meskipun tanda dan gejala penyakit mereka sama dengan yang Anda alami.
- Apabila Anda mengalami efek samping, komunikasikanlah pada dokter atau apoteker Anda. Perhatikan pula kemungkinan efek samping yang tidak terdaftar dalam leaflet ini.

Informasi yang terkandung dalam leaflet ini :

1. Nama Produk

ENVLO

2. Bentuk Sediaan

Tablet Salut Selaput

3. Deskripsi Produk

Tablet salut selaput, bikonveks, berbentuk segitiga, berwarna jingga pucat dengan huruf “E” di satu sisi dan “03” di sisi lainnya.

4. Apa saja kandungan produk ini?

Envlo mengandung zat aktif Enavogliflozin.

5. Kekuatan

Tiap tablet salut selaput mengandung 0,3 mg Enavogliflozin.

6. Untuk apa produk ini digunakan?

ENVLO mengandung zat aktif enavogliflozin yang merupakan golongan obat antidiabetik yang diberikan secara oral untuk menurunkan kadar gula darah.

ENVLO diindikasikan pada pasien dengan diabetes melitus tipe 2 untuk meningkatkan kontrol glikemik dalam kombinasi dengan metformin, ketika metformin, bersama dengan diet dan olahraga, tidak memberikan kontrol kadar gula darah yang memadai.

7. Seberapa banyak dan seberapa sering Anda harus menggunakan obat ini? Apa yang harus Anda lakukan jika Anda lupa minum satu dosis?

Dosis ENVLO yang direkomendasikan adalah 0,3 mg sekali sehari sebagai terapi kombinasi tambahan dengan metformin. Tablet dapat diminum dengan atau tanpa makanan, ditelan utuh dengan air.

Untuk pasien dengan Gangguan Ginjal: Konsultasikan dengan dokter Anda sebelum menggunakan Enavogliflozin. Dokter perlu melakukan pemeriksaan fungsi ginjal Anda sebelum memutuskan terapi yang sesuai untuk Anda.

8. Kapan Anda tidak boleh menggunakan produk ini?

Jangan menggunakan ENVLO apabila:

- Anda memiliki riwayat alergi serius terhadap Enavogliflozin atau bahan-bahan lain yang terkandung dalam obat ini.
- Anda mengidap diabetes tipe 1 atau ketoasidosis diabetikum.
- Anda memiliki nilai laju filtrasi glomerular (eGFR) kurang dari 30 mL/menit/1,73m^2, penyakit ginjal stadium akhir atau dialisis.
- Anda mengalami gangguan hati sedang dan berat.

9. Apa yang harus diperhatikan saat Anda menggunakan produk ini?

Diskusikan dengan dokter, perawat, atau apoteker Anda sebelum mengkonsumsi ENVLO:

- Apabila Anda mengalami penurunan volume cairan tubuh dan gangguan fungsi ginjal
- Apabila Anda mengalami gagal jantung
- Apabila Anda mengalami gangguan hati
- Apabila Anda mengalami malnutrisi, kelaparan, kebiasaan makan yang tidak teratur, asupan makanan yang tidak mencukupi atau hipostenia
- Apabila Anda mengalami ketoasidosis
- Apabila Anda mengidap infeksi saluran kemih dan infeksi genital
- Apabila Anda memiliki risiko kekurangan cairan atau dehidrasi

Anak-anak dan remaja

ENVLO tidak direkomendasikan untuk digunakan oleh anak dan remaja di bawah 18 tahun karena belum ada penelitian Envlo untuk kelompok usia tersebut.

Lansia

- ENVLO harus diberikan dengan perhatian pada pasien lanjut usia
- ENVLO tidak direkomendasikan untuk digunakan oleh lansia di atas 80 tahun karena keterbatasan pengalaman penggunaan obat ini pada pasien demikian.

Fungsi ginjal

Obat ini tidak direkomendasikan untuk digunakan oleh pasien dengan gangguan fungsi ginjal yang

parah dengan laju filtrasi glomerular kurang dari 60 mL/menit/1,73 m^2.
Jika nilai eGFR konsisten kurang dari 60 mL/menit/1,73m^2 maka obat harus dihentikan.

Fungsi hati
Obat ini harus diberikan dengan perhatian pada pasien dengan gangguan fungsi hati.

10. Apa saja obat atau makanan lain yang harus dihindari selama penggunaan obat ini?
Konsultasikan dengan dokter, perawat, atau apoteker Anda apabila Anda sedang menggunakan, akan menggunakan, atau telah menggunakan obat selain ENVLO.

11. Kehamilan dan Menyusui
ENVLO tidak dianjurkan diberikan pada wanita yang sedang hamil atau menyusui. Konsultasikan kepada dokter Anda sebelum menggunakan ENVLO apabila Anda sedang atau merencanakan untuk hamil, atau sedang menyusui.

12. Berkendara dan Menggunakan Mesin
Gejala hipoglikemia dapat terjadi. Anda dianjurkan untuk melakukan tindakan pencegahan agar terhindar dari hipoglikemia saat mengemudi dan menggunakan mesin.

13. Apa saja efek samping yang mungkin terjadi akibat penggunaan produk ini?
Sama seperti obat pada umumnya, obat ini dapat menimbulkan efek samping walaupun tidak semua orang akan mengalaminya.

Efek samping yang dapat terjadi antara lain:
- Gangguan saluran cerna: gangguan/rasa tidak nyaman di pencernaan (dyspepsia), radang lambung (gastritis) dan gastritis kronik, refluks saluran cerna (GERD), kantung kecil pada saluran (diverticulum) usus, luka pada anus (fisura), polip usus besar, usus mekanik, mual
- Infeksi dan infeksi parasit: infeksi vaginal, infeksi saluran napas atas/nasofaring, infeksi kandung kemih (sistitis), tuberkulosis tidak aktif (laten), infeksi Covid-19, infeksi virus pada kulit, radang pada gusi (periodontitis), radang pada saluran sinus (sinusitis)
- Gangguan muskuloskeletal dan jaringan ikat: nyeri sendi, nyeri otot, kista jaringan sinovial, kelainan pada cakram tulang belakang, pembengkokan tulang belakang (scoliosis), nyeri pada jaringan penghubung bagian belakang kepala dengan rahang bawah (temporomandibular), nyeri pada bagian belakang/punggung, nyeri pada leher, nyeri pada bagian pundak/bahu
- Cedera, keracunan, atau komplikasi prosedur: robekan pada kulit, fraktur (patah/retak) tulang kaki, fraktur tulang kering, dislokasi sendi, memar, pingsan
- Gangguan sistem saraf: sakit kepala, kebas pada area tertentu, kelumpuhan wajah
- Gangguan metabolism dan nutrisi: gangguan kadar lemak (dislipidemia), gula darah rendah (hipoglikemia), kadar lemak lebih tinggi dari normal (hiperlipidemia)
- Gangguan sistem reproduksi dan payudara: disfungsi seksual
- Gangguan pada ginjal dan saluran urin: darah pada urin (hematuria)
- Gangguan fungsi hati dan kelenjar empedu: batu empedu, fungsi hati abnormal
- Gangguan jantung: sakit dada tiba-tiba (angina) dan tidak stabil
- Gangguan umum dan kondisi pada tempat pemberian obat: nyeri dada (umum)
- Jaringan tumbuh abnormal (neoplasma) jinak, ganas, dan tidak spesifik (termasuk kista dan polip): tumor jinak pada usus besar
- Tumor jaringan mukosa lambung-usus, jaringan saraf abnormal (neuroma)
- Gangguan pernapasan, toraks, dan rongga dada (mediastinum): gangguan pada suara (disfonia), bernapas telalu cepat/terlalu dalam (hiperventilasi)
- Gangguan pembuluh darah/vaskular: penebalan/penonjolan pembuluh vena (varises), penebalan pembuluh arteri (arteriosclerosis), tekanan darah tinggi (hipertensi)
- Gangguan psikiatrik: susah tidur (insomnia)

- Gangguan sistem imun: alergi makanan
- Gangguan sistem endokrin/hormon: kelenjar tiroid mengecil (hipotiroidisme), kista atau massa pada kelenjar tiroid
- Gangguan penglihatan: katarak
- Gangguan kulit dan jaringan bawah kulit: biduran (urtikaria)

Segera konsultasikan dengan dokter, apoteker, atau tenaga kesehatan apabila Anda mengalami salah satu atau lebih gejala efek samping di atas.

Laporkan efek samping yang Anda alami kepada Industri Farmasi pemilik izin edar dengan informasi sebagai berikut:

PT Daewoong Pharmaceutical Indonesia
WeWork Revenue Tower 20th Floor SCBD, Lot 13 District 8, Jl. Jenderal Sudirman Kav. 52-53 RT. 5 RW.3, Senayan, 12190

24-hour Pharmacovigilance Unit
Phone: +62 889-7580-0212
Email: safety_dwi@daewoong.co.kr
Website: https://daewoongpharm.id/

14.A pa yang harus saya lakukan jika saya mengonsumsi lebih dari dosis yang dianjurkan?
Segera hubungi dokter Anda apabila Anda mengonsumsi lebih dari dosis yang dianjurkan dan mengalami gejala hipoglikemia seperti pusing, keringat dingin, jantung berdebar, pucat, mudah marah, lapar, dan sulit berkonsentrasi.

15.B agaimana cara menyimpan obat ini?
Simpan di bawah suhu 30ºC dalam wadah kedap udara, jauhkan dari jangkauan anak-anak.

16. Bahan Tambahan Obat
ENVLO mengandung bahan tambahan obat sebagai berikut: *Microcrystalline cellulose, Colloidal silicon dioxide, Hydroxypropylcellulose, Magnesium Stearate, Croscarmellose sodium, Hypromellose 2910, Titanium dioxide, Polyethylene glycol 400, Iron oxide yellow, Iron oxide red*

17.N omor izin edar (NIE)
ENVLO, 0.3 mg Tablet Salut Selaput, Dus, 3 blister@10 Tablet Salut Selaput,
No. Reg.

18.N ama dan alamat produsen dan pemegang izin edar
Diproduksi oleh:
Daewoong Pharmaceutical Co., Ltd.
Cheongju-si, Republic of Korea

Diimpor dan dipasarkan oleh:
PT Daewoong Pharmaceutical Indonesia, Cikarang, Indonesia
Phone: +62 21 3972 1100
https://daewoongpharm.id/

19. Tanggal Revisi Leaflet Pasien
23 Desember 2025

HARUS DENGAN RESEP DOKTER