ENVLO® 0.3 mg film-coated tablets

(ENAVOGLIFLOZIN)

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 of Enavogliflozin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ENVLO 0.3 mg film-coated tablet is a pale-orange, biconvex, triangular, film-coated tablet with “D” on one side and “I3” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENVLO is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

4.2 Posology and method of administration

Posology

The recommended dose of Enavogliflozin is 0.3 mg once daily, for use as monotherapy and in combination therapy with other glucose lowering (or hypoglycaemic) agents [Refer to Section 5.1 Pharmacodynamic properties].

Special Populations

Renal impairment

The effectiveness of this drug depends on renal function, and safety and efficacy have not been established in patients with moderate to severe renal impairment. Treatment with this drug should not be initiated in patients with eGFR less than 60 mL/min/1.73 m^2. If the eGFR is consistently less than 60 mL/min/1.73 m^2, this drug should be discontinued. No dose adjustment is necessary for patients with mild renal impairment.

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

Pediatric population

The clinical safety and efficacy of Enavogliflozin in children and adolescents have not been established

Geriatrics

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 is not recommended.

Method of administration

The tablets can be taken with or without food, swallowed whole with water

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4.3 Contraindications

Do not administer in the following patients.

a) History of serious hypersensitivity reaction to Enavogliflozin or any of its components
b) Type 1 diabetes or diabetic ketoacidosis
c) eGFR of less than 30 mL/min/1.73m^2, end-stage renal disease (ESRD) or dialysis
d) Moderate and severe hepatic impairment

4.4 Special warnings and precautions for use

Administration in patients with decreased volume of body fluid and impaired renal function

Diuretic effects of SGLT2 inhibitors may cause polyuria and frequent urination, and osmotic diuresis accompanying glucosuria 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.

Enavogliflozin may also 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 and be monitored for hypotensive symptoms and signs and renal function thereafter. As efficacy of Enavogliflozin depends on renal function and 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:

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

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.

Patients with Hepatic impairment

Since experience in patients with mild hepatic impairment is limited, it should be used with caution in these patients.

Hypoglycaemia

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

Following patients or conditions may cause hypoglycaemia, therefore, attention is required for the occurrence of hypoglycaemia:

a) Combination with insulin secretagogues such as insulin and sulfonylureas
b) Hypopituitarism or adrenal insufficiency
c) Malnutrition, starvation, irregular eating habits, insufficient of food intake or hyposthenia
d) Patients who muscle exercise vigorously
e) Excessive alcohol intake

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), due to increased fatty acid metabolism, 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. Ketoacidosis can occur without a significant increase in blood glucose, especially in patients with reduced insulin secretion (such as type 1 diabetes mellitus, pancreatitis or a history of pancreatic surgery), dose reduction or discontinuation of insulin preparations, acute febrile illness, excessive restriction of carbohydrate intake, poor dietary intake, infection, and/or dehydration and alcohol abuse. Patients should be provided with information about symptoms of ketoacidosis (such as nausea and vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnea and/or decreased consciousness) and if these symptoms are observed, the patient should be instructed to visit a medical institution immediately.

If ketoacidosis is suspected or clinical conditions likely to induce ketoacidosis (e.g., prolonged fasting due to acute illness and surgery) occur, 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.

Urinary Tract and Genital Infections

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 these agents to these patients.

In addition, Enavogliflozin may increase the risk of or worsen urinary tract and genital infections (including mycotic). 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 Section 4.8 Undesirable effects].

Serious urinary tract infections, including urosepsis and pyelonephritis have been also reported post-marketing in patients using other SGLT2 inhibitors. Accordingly, these symptoms should be monitored and treated appropriately. 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. Patients taking Enavogliflozin will test positive for glucose in urine due to its mechanism of action.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

a) Enavogliflozin is mainly metabolized by cytochrome P450 (CYP) 3A4. *In vitro* studies have shown that neither Enavogliflozin nor its active metabolite M1 inhibit CYP isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) or UGT isoenzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7). No induction effect was observed for CYP3A4, CYP1A2, and CYP2B6.

   Furthermore*, in vitro* studies demonstrated that Enavogliflozin is a substrate for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and P-gp but does not inhibit OCT1, OCT2, OAT1, or BCRP transporters. Similarly, its active metabolite M1 did not inhibit OAT1, OAT3, OATP1B1, NTCP, P-gp, and BCRP.

b) No clinically significant pharmacokinetic interaction was observed when Enavogliflozin was administered in combination with metformin or in combination with metformin and gemigliptin.

   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 (Cmax) of Enavogliflozin increased by 21%, but the area under the blood concentration-time curve (AUC) did not change.

   Metformin and Gemigliptin

   When 2 mg of Enavogliflozin, 1000 mg of Metformin, and 50 mg of Gemigliptin were co-administered, the pharmacokinetic properties of Metformin and Gemigliptin did not change, and the Cmax of Enavogliflozin increased by 27%, but the AUC did not change.

c) Concomitant use of SGLT2 inhibitor and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

4.6 Fertility, pregnancy and lactation

Fertility

The effect of enavogliflozin on fertility in humans has not been studied. In male and female rats, enavogliflozin showed no effects on fertility at any dose tested.

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. Embryo-fetal development studies in rats and rabbits showed decreased maternal weight gain, with no observed effects on embryo-fetal development (Transfer to the fetuses has been reported in rat studies).

Lactation

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

4.8 Undesirable effects

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 clinical trials, one monotherapy clinical trial was conducted for 24 weeks, and the safety and efficacy of long-term administration were evaluated for 52 weeks. Two combination therapy clinical trials (metformin, metformin and gemigliptin) were conducted for 24 weeks, and among these, the metformin combination therapy clinical trial evaluated the safety and efficacy of long-term administration for 52 weeks.

A total of 836 patients with type 2 diabetes were included in four clinical trials (one phase 2 and three phase 3) to evaluate the safety of Enavogliflozin. Among patients who participated 12- or 24-week duration, 134 patients received placebo, 235 patients received active control, and 467 patients were treated with Enavogliflozin.

List of adverse events

a) The safety and tolerability of Enavogliflozin were evaluated through a predefined pooled analysis of placebo- controlled trials; one phase 2 clinical trial and one phase 3 clinical trial (one monotherapy). Adverse reactions reported in patients treated with placebo or Enavogliflozin are listed in Table 1, classified by system organ class (SOC) and MedDRA terms.

Table 1. The adverse reactions reported in placebo-controlled studies[a, b]

	Enavogliflozin N=232 (%)	Placebo N=134 (%)
Gastrointestinal disorders		
Dyspepsia	2 (0.86)*	1 (0.75)
Constipation	1 (0.43)*	0
Gastritis	1 (0.43)	0
Abdominal pain upper	1 (0.43)	1 (0.75)
Abdominal pain	2 (0.86)	0
Gastric polyps	0	1 (0.75)
Diarrhoea	1 (0.43)	0
Dry mouth	1 (0.43)*	0
Enterocolitis	1 (0.43)	0
Haematochezia	1 (0.43)	0

Parotid gland enlargement	0	1 (0.75)
Infections and infestations		
Vaginal infection	3 (1.29)*	0
Nasopharyngitis	1 (0.43)	2 (1.49)
Periodontitis	1 (0.43)	1 (0.75)
Cystitis	1 (0.43)*	0
Herpes zoster	0	2 (1.49)
Latent tuberculosis	1 (0.43)	0
Upper respiratory tract infection	1 (0.43)	1 (0.75)
Anal abscess	1 (0.43)	0
Folliculitis	1 (0.43)	0
Ophthalmic herpes zoster	0	1 (0.75)
Pyelonephritis	1 (0.43)*	0
Tinea pedis	1 (0.43)	0
Urinary tract infection	0	1 (0.75)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (0.86)	0
Back pain	1 (0.43)	1 (0.75)
Intervertebral disc degeneration	1 (0.43)	1 (0.75)
Spinal osteoarthritis	1 (0.43)	0
Cervical stenosis	1 (0.43)	0
Groin pain	1 (0.43)	0
Musculoskeletal chest pain	1 (0.43)	0
Spinal stenosis	1 (0.43)	0
Trigger finger	0	1 (0.75)
Injury, poisoning and procedural complications		
Contusion	2 (0.86)	0
Ligament rupture	2 (0.86)	0
Ligament sprain	2 (0.86)	0
Wrist Fracture	1 (0.43)	0
Arthropod bite	1 (0.43)	0
Epicondylitis	1 (0.43)	0
Muscular strain	1 (0.43)	0
Sternal fracture	0	1 (0.75)
Nervous system disorders		
Headache	1 (0.43)	0
Dizziness	1 (0.43)	0
Hypoaesthesia	0	1 (0.75)
Paraesthesia	2 (0.86)	0
Skin and subcutaneous tissue disorders		
Mechanical urticaria	1 (0.43)	0
Psoriasis	0	1 (0.75)
Skin ulcer	0	1 (0.75)

Metabolism and nutrition disorders		
Dyslipidaemia	2 (0.86)*	1 (0.75)
Hyperlipidaemia	1 (0.43)	0
Reproductive system and breast disorders		
Benign prostatic hyperplasia	2 (0.86)	1 (0.75)
Pruritus genital	2 (0.86)*	0
Cervical polyp	1 (0.43)	0
Genital erythema	1 (0.43)*	0
Renal and urinary disorders		
Dysuria	1 (0.43)*	0
Nocturia	1 (0.43)*	1 (0.75)
Pollakiuria	0	1 (0.75)
Polyuria	1 (0.43)*	0
Hepatobiliary disorders		
Hyperbilirubinaemia	0	1 (0.75)
Cardiac disorders		
Cardiomegaly	1 (0.43)	0
General disorders and administration site conditions		
Pain	0	1 (0.75)
Condition aggravated	1 (0.43)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Uterine leiomyoma	0	1 (0.75)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (0.43)	0
Respiratory disorder	1 (0.43)	0
Rhinorrhoea	0	1 (0.75)
Investigations		
Aspartate aminotransferase increased	1 (0.43)*	1 (0.75)
Blood triglycerides increased	0	2 (1.49)
Alanine aminotransferase increased	1 (0.43)*	0
Blood creatine phosphokinase increased	0	1 (0.75)
Gamma-glutamyltransferase increased	0	1 (0.75)
Eye disorders		
Cataract	0	1 (0.75)
Dry eye	0	1 (0.75)
Blood and lymphatic system disorders		
Polycythaemia	2 (0.86)	0
Anaemia	1 (0.43)	0
Myelosuppression	1 (0.43)*	0
Vascular disorders		
Hypertension	1 (0.43)	0
Orthostatic hypotension	1 (0.43)	0
Psychiatric disorders		

Insomnia	1 (0.43)	1 (0.75)
Anxiety	1 (0.43)	0
Endocrine disorders		
Thyroiditis subacute	1 (0.43)	0

a. Drug adverse reactions that cannot be excluded from the causal relationship with Enavogliflozin were marked with (adverse reaction name*).

b. This is the combined analysis result of two placebo-controlled trials; one phase 2 clinical trial and one phase 3 clinical trial (one monotherapy). Adverse reactions that occurred after taking Enavogliflozin or all dose groups were presented. The phase 2 clinical trial was conducted for 12 weeks, and the phase 3 clinical trial (monotherapy) was conducted for 24 weeks.

b) In two phase 3 clinical trials (metformin combination therapy, and metformin and gemigliptin 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 2.

Table 2. Adverse reactions reported at ≥ 1% in active control combination clinical trials (24 weeks Clinical trials)[a]

	Metformin combination[b]		Metformin / Gemigliptin combination[b]	
	Enavogliflozin N=101 (%)	Dapagliflozin N=99 (%)	Enavogliflozin N=134 (%)	Dapagliflozin N=136 (%)
Gastrointestinal disorders				
Dyspepsia	1 (0.99)	2 (2.02)*	0	1 (0.74)
Constipation	0	1 (1.01)	2 (1.49)	1 (0.74)
Gastritis	0	2 (2.02)	1 (0.75)	0
Abdominal pain upper	0	2 (2.02)	0	0
Gastroesophageal reflux disease	0	2 (2.02)	0	0
Toothache	0	0	2 (1.49)	0
Vomiting	0	1 (1.01)	0	0
Infections and infestations				
Vaginal infection	0	0	2 (1.49)*	2 (1.47)*
Cystitis	1 (0.99)*	1 (1.01)*	0	0
Tonsillitis	0	1 (1.01)	0	0
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0.99)	1 (1.01)	0	1 (0.74)
Myalgia	1 (0.99)	1 (1.01)	0	1 (0.74)
Pain in extremity	0	0	1 (0.75)	2 (1.47)
Musculoskeletal discomfort	0	0	0	2 (1.47)
Nervous system disorders				
Headache	2 (1.98)	2 (2.02)	0	0
Dizziness	0	1 (1.01)	0	3 (2.21)
Skin and subcutaneous tissue disorders				
Pruritus	0	2 (2.02)*	2 (1.49)*	1 (0.74)*
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 (0.75)	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				
Hepatic steatosis	0	2 (2.02)	0	0
Hepatitis toxic	0	0	2 (1.49)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
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	0
Blood and lymphatic system disorders				
Leukocytosis	0	1 (1.01)	0	0

a. Drug adverse reactions that cannot be excluded from the causal relationship with Enavogliflozin and its active control dug 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 are the analysis results of phase 3 clinical trials of metformin combination therapy and metformin and gemigliptin combination therapy, and the two trials were conducted as active control clinical trials for 24 weeks.

c) 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 by 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 infestations: cystitis*, COVID-19, periodontitis, sinusitis
- Various immune system disorders: food allergy
- Various endocrine disorders: hypothyroidism, thyroid cyst, thyroid mass
- Various eye disorders: cataract
- Various vascular disorders: arteriosclerosis, hypertension
- Various gastrointestinal disorders: dysepsia, 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: hematuria
- Reproductive system and breast disorders: sexual dysfunction
- Injury, poisoning and procedural complications: contusion, concussion

d) In the phase 3 clinical trial of metformin and gemigliptin combination therapy conducted for 24 weeks, the adverse reactions reported in less than 1% in the drug-administered group are listed by 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 infestations: gastroenteritis, periodontitis
- Neoplasms benign, malignant and unspecified (incl cysts and polyps): intraductal papilloma of breast
- Metabolism and nutrition disorders: hypoglycaemia
- Various nervous system disorders: lethargy*, somnolence*
- Ear and labyrinth disorders: vertigo positional
- Various heart disorders: angina pectoris, palpitations
- Respiratory, thoracic, and mediastinal disorders: dyspnoea
- Various gastrointestinal disorders: abdominal pain lower, gastritis, pancreatic cyst
- Hepatobiliary disorders: cholelithiasis

- Skin and subcutaneous tissue disorders: alopecia, miliaria
- Musculoskeletal and connective tissue disorders: pain in extremity, calcification of muscle, flank pain, spinal osteoarthritis
- Renal and urinary disorders: dysuria
- Reproductive system and breast disorders: dysmenorrhea, vaginal haemorrhage
- General disorders and administration site conditions: asthenia
- Clinical investigations: blood pressure decreased*, blood pressure increased
- Injury, poisoning and procedural complications: fall, skin laceration

e) Adverse reactions reported at a rate of 1% or more in the monotherapy extension trial and the metformin combination therapy extension study (25-52 weeks) were classified by system organ class (SOC) and MedDRA terms and are shown in Table 3.

Table 3. Adverse reactions reported by more than 1% in monotherapy and metformin combination clinical trial extension studies

	Monotherapy extension study[b]		Metformin combination extension study[c]	
	Maintenance group[d] N=37(%)	Switching group[e] N=26(%)	Maintenance group[f] N=82(%)	Switching group[g] N=77(%)
Gastrointestinal disorders				
Chronic gastritis	1(2.70)	0	1(1.22)	0
Colitis	0	1(3.85)	0	0
Diverticulum intestinal	0	0	1(1.22)	0
Dyspepsia	1(2.70)	0	0	0
Gastritis	0	0	1(1.22)	0
Gastroesophageal reflux disease	0	0	0	1(1.30)
Mechanical ileus	0	0	1(1.22)	0
Infections and infestations				
COVID-19	1(2.70)	2(7.69)	2(2.44)	0
Nasopharyngitis	1(2.70)	0	1(1.22)	0
Coronavirus infection	0	0	1(1.22)	0
Herpes zoster	0	1(3.85)	0	0
Latent tuberculosis	0	0	0	1(1.30)
Periodontitis	1(2.70)	0	0	0
Vaginal infection	0	0	1(1.22)*	0
Viral skin infection	0	0	0	1(1.30)
Musculoskeletal and connective tissue disorders				
Arthralgia	1(2.70)	0	0	1(1.30)
Back pain	0	1(3.85)	0	0
Intervertebral disc disorder	0	0	0	1(1.30)
Intervertebral disc protrusion	1(2.70)	0	0	0
Myalgia	0	0	0	1(1.30)
Scoliosis	0	0	0	1(1.30)
Synovial cyst	0	0	1(1.22)	0
Injury, poisoning and procedural complications				
Epicondylitis	0	1(3.85)	0	0
Foot fracture	0	0	1(1.22)	0
Joint dislocation	0	0	0	1(1.30)
Skin lacerations	0	0	0	1(1.30)
Tibia fracture	0	0	0	1(1.30)
Nervous system disorders				
Facial paralysis	0	0	0	1(1.30)
Headache	0	0	0	1(1.30)
Hypoaesthesia	0	0	1(1.22)	0
Skin and subcutaneous tissue disorders				

Ingrowing nail	0	1(3.85)	0	0
Urticaria	0	1(3.85)	0	0
Metabolism and nutrition disorders				
Hypoglycaemia	0	0	1(1.22)	2(2.60)*
Hyperlipidaemia	0	0	1(1.22)	0
Reproductive system and breast disorders				
Benign prostatic hyperplasia	0	1(3.85)	0	0
Pruritus genital	0	1(3.85)	0	0
Renal and urinary disorders				
Glomerulonephritis membranous	0	1(3.85)	0	0
Hepatobiliary disorders				
Cholelithiasis	0	0	1(1.22)	0
Cardiac disorders				
Angina unstable	0	0	1(1.22)	0
Myocarditis	0	0	0	1(1.30)
General disorders and administration site conditions				
Chest pain	0	0	0	1(1.30)
Psychiatric disorders				
Insomnia	0	0	1(1.22)	0
Neoplasms benign, malignant and unspecified(incl cysts and polyps)				
Benign breast neoplasm	1(2.70)	0	0	0
Colon adenoma	0	0	1(1.22)	0
Gastrointestinal submucosal tumor	0	0	1(1.22)	0
Neuroma	0	0	1(1.22)	0
Vascular disorders				
Varicose vein	0	0	1(1.22)	0

a. The incidence of adverse reactions in all groups for adverse reactions reported at 1% or more in any one group was described. Drug adverse reactions that cannot be excluded from the causal relationship with Enavogliflozin and its active control drug were marked with (adverse reaction name*)

b. 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 monotherapy.

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

e. Switching group: 0-24 weeks placebo, 25-52 weeks Enavogliflozin 0.3 mg administration

f. Maintenance groups: 0-24 weeks Enavogliflozin 0.3 mg, 25-52 weeks Enavogliflozin 0.3 mg administration (metformin administration continued.)

g. Switching group: 0-24 weeks dapagliflozin 10 mg, 25-52 weeks Enavogliflozin 0.3 mg administration (metformin administration continued)

Description of particular adverse reactions

Hypoglycaemia

During the extended period (25 to 52 weeks) of metformin combination therapy out of four clinical trials, hypoglycaemia was reported in 3 patients (1.89%) in the Enavogliflozin group. In a phase 3 clinical trial of metformin and gemigliptin combination therapy, hypoglycaemia was reported in 1 patient (0.75%) in the Enavogliflozin-treated group.

Urinary tract and genital infections

There were no adverse reactions reported as urinary tract infections in the Enavogliflozin-treated group in the the six clinical trials (one Phase II study, three Phase III 24-week study, two Phase III extension study). According to the integrated safety analysis of placebo-controlled trials including one phase 2 clinical trial and and one monotherapy phase 3 clinical trial, vaginal infection occurred in 3 patients (1.29%), cystitis in 1 patient (0.43%),

and pyelonephritis in 1 patient (0.43%) in Enavogliflozin-treated group. In the active control clinical trials, 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. Vaginal infection was reported in 2 patients (1.49%) in the metformin-gemigliptin combination therapy phase 3 clinical trial.

Pollakiuria and Polyuria

There were no adverse reactions reported as pollakiuria in the Enavogliflozin-treated group among the six clinical trials (one Phase II study, three Phase III 24-week study, two Phase III extension study). According to an integrated safety analysis of placebo-controlled trials including one phase 2 clinical trial and one monotherapy phase 3 clinical trial, polyuria was reported in 1 patient (0.43%) in the Enavogliflozin-treated group

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, hypoglycaemia, 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

Pharmacotherapeutic group: Drug used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK09 enavogliflozin

Mechanism of Action:

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 loses weight. When compared with SGLT-1, the major cotransporter involved in glucose reabsorption in the gastrointestinal tract, Enavogliflozin selectively inhibited human SGLT2. The inhibitory concentration (IC_{50}) of SGLT-1 was 436 nmol/L and SGLT2 was 0.43 nmol/L (*in vitro*).

Clinical efficacy and safety

Monotherapy

A double-blind, placebo-controlled study was conducted for 24 weeks in type 2 diabetic patients whose blood sugar levels were not adequately controlled by diet and exercise alone. Administration of Enavogliflozin significantly reduced HbA1c compared to the placebo (P<0.0001) [Refer to Table 4]. Afterwards, in the extended period of the trial, which lasted up to 52 weeks, the effect of reducing blood sugar compared to baseline at week 24 was observed to be maintained until week 52 in the group that maintained 0.3 mg of Enavogliflozin.

Table 4. Efficacy results at 24 week compared to placebo when Enavogliflozin was administered alone

Efficacy Endpoint	Enavogliflozin 0.3 mg	Placebo
The primary endpoint: HbA1c (%)		
Number of subjects[a]	82	79
HbA1c (%) baseline mean (SD)	7.64(0.66)	7.72(0.63)
Difference from baseline after 24 weeks (LS Mean	-0.88(0.10)	0.11(0.11)

(SE))[b,c]		
Difference from Placebo [95% CI][b,c]	-0.99* [-1.24, -0.74]	
Percent of patients achieving HbA1c <7% (%)	70.7%*	24.1%
Percent of patients with achieving greater than 0.5% reduction in HbA1c or achieving HbA1c <7% (%)	82.9%*	31.6%

a: Full Analysis Set (FAS)

b: LOCF: last observation (prior to rescue for rescued patients) carried forward.

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

* p-value <0.0001

Combination Therapy

a) Clinical Trials of Combination Therapy with Metformin

These clinical studies investigate the add-on combination therapy of Enavogliflozin to the monotherapy of Metformin. 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 hydrochloride (≥1000mg/day), 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 [Refer to Table 5]. 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 [Refer to Table 6].

Table 5. Efficacy results at 24 week compared to placebo when Enavogliflozin was co-administered with metformin

HbA1c (%)	Metformin + Enavogliflozin 0.3mg	Metformin + Dapagliflozin 10mg
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 6. 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, c]	-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 Enavogliflozin 10 mg, 25-52 weeks Enavogliflozin 0.3 mg administration (metformin administration continued)

a: Full Analysis Set (FAS)
b: LOCF: last observation (prior to rescue for rescued patients) carried forward.
c: ANCOVA (analysis of covariance) (model includes stratification factor and baseline HbA1c as covariates and treatment group as a factor)

b) Clinical trials of Combination Therapy with Metformin and Gemigliptin

These clinical studies investigate the add-on combination therapy of Enavogliflozin to Metformin and Gemigliptin. In a clinical trial 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 the metformin (≥1000mg/day) and gemigliptin (50mg), compared to the dapagliflozin group (metformin, gemigliptin, and dapagliflozin), the HbA1c change value of the 0.3 mg group (metformin, gemigliptin, and Enavogliflozin) was statistically non-inferior.

Table 7. Efficacy results at 24 weeks compared to the reference drug when metformin and gemigliptin were co- administered with Enavogliflozin

HbA1c (%)	Metformin + Gemigliptin + Enavogliflozin 0.3 mg	Metformin + Gemigliptin + Dapagliflozin 10 mg
The primary endpoint: HbA1c (%)		
Number of subjects[a]	119	123
HbA1c (%) baseline mean (SD)	7.79(0.77)	7.83(0.81)
Difference from baseline after 24 weeks (LS Mean (SE))[b]	-0.92(0.05)	-0.86(0.05)
Difference from metformin + gemigliptin + dapagliflozin [95% CI][a]	-0.06[-0.19, 0.06][c]	
Percent of patients achieving HbA1c <7% (%)	66.4%	62.6%
Percent of patients with achieving greater than 0.5% reduction in HbA1c or achieving HbA1c <7% (%)	86.6%	85.4%

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%

5.2 Pharmacokinetic properties

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.

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*).

Metabolism

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*). Therefore, no drug interactions involving the major CYP450 and UGT isozymes are expected when enavogliflozin and substrate drugs of these enzymes are co-administered.

Excretion

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.

Special Population

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 three phase 3 clinical trials of Enavogliflozin.

Elderly

Of the 318 patients who took Enavogliflozin at least once in three phase 3 clinical trials of Enavogliflozin, 219(68.9%) were under the age of 65, 99(31.1%) were over the age of 65, and 18(5.7%) were over the age of 75. As a result of subgroup analysis for each 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

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.

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

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.

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.

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 are both 10 mg/kg/day, which is 776 times higher than the recommended human exposure (0.3 mg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Silica, colloidal anhydrous
Hydroxypropylcellulose
Magnesium Stearate
Croscarmellose sodium

Film coating

Alcohol*
Hypromellose 2910
Titanium dioxide
Polyethylene glycol 400
Iron oxide yellow
Iron oxide red
Purified water**

* Alcohol is removed during the production process, controlled to not more than 0.5% of ethanol
** Purified water is removed during the production process

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C in original packaging.

6.5 Nature and contents of container

Each Aluminium-aluminium blister pack contains 10 tablets. Three blister packs are supplied per carton (total of 30 tablets per carton**).**

7. PRODUCT REGISTRATION HOLDER

Taevas Life Sciences Sdn. Bhd.
Suite 163E, Level 16, Gurney Paragon Office Tower, Jalan Kelawei, 10250 George Town, Pulau Pinang, Malaysia

8. MANUFACTURER

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9. DATE OF REVISION

October 2025