1. NAME OF THE MEDICINAL PRODUCT

Steglujan® 5/100 mg tablets
Steglujan® 15/100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Steglujan 5/100 mg tablets
Each tablet contains 5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 100 mg sitagliptin (as sitagliptin phosphate monohydrate).

Steglujan 15/100 mg tablets
Each tablet contains 15 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) and 100 mg sitagliptin (as sitagliptin phosphate monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Steglujan 5/100 mg tablets
Beige, almond-shaped, film-coated tablets debossed with "554" on one side and plain on the other side.

Steglujan 15/100 mg tablets
Brown, almond-shaped, film-coated tablets debossed with "555" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Steglujan is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- when metformin and/or a sulphonylurea (SU) and one of the monocomponents of Steglujan do not provide adequate glycaemic control.
- in patients already being treated with the combination of ertugliflozin and sitagliptin as separate tablets.

(For study results with respect to combinations and effects on glycaemic control, see sections 4.4, 4.5, and 5.1)

4.2 Posology and method of administration

Posology
The recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily. In patients tolerating the starting dose, the dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin, once daily, if additional glycaemic control is needed.

For patients treated with ertugliflozin who are being switched to Steglujan, the dose of ertugliflozin can be maintained.

When Steglujan is used in combination with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia (see sections 4.4, 4.5, and 4.8).

In patients with volume depletion, correcting this condition prior to initiation of Steglujan is recommended (see section 4.4).

If a dose is missed, it should be taken as soon as the patient remembers. Patients should not take two doses of Steglujan on the same day.

Special populations

Renal impairment
Assessment of renal function is recommended prior to initiation of Steglujan and periodically thereafter (see section 4.4).

Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 or CrCl less than 60 mL/min (see section 4.4).

Steglujan should be discontinued when eGFR is persistently less than 45 mL/min/1.73 m^2 or CrCl is persistently less than 45 mL/min.

The fixed-dose combination of ertugliflozin and sitagliptin should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis. Ertugliflozin is not expected to be effective in these patients.

Hepatic impairment
No dose adjustment of Steglujan is necessary in patients with mild or moderate hepatic impairment. Steglujan has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients (see section 5.2).

Elderly (≥ 65 years old)
No dose adjustment of Steglujan is recommended based on age. Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and sitagliptin is known to be substantially excreted by the kidneys, renal function should be assessed more frequently in elderly patients. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 4.8). There is limited experience with Steglujan in patients ≥ 75 years of age.

Paediatric population
The safety and efficacy of Steglujan in children under 18 years of age have not been established. No data are available.

Method of administration
Steglujan should be taken orally once daily in the morning, with or without food. In case of swallowing difficulties, the tablet could be broken or crushed as it is an immediate-release dosage form.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Steglujan should not be used in patients with type 1 diabetes mellitus.

Acute pancreatitis
Use of dipeptidyl peptidase-4 (DPP-4) inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Steglujan and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Steglujan should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Heart Failure
An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of sitagliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of sitagliptin.

Hypotension/Volume depletion
Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Steglujan (see section 4.8), particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2 or CrCl less than 60 mL/min), elderly patients (≥ 65 years), patients on diuretics, or patients on anti-hypertensive therapy with a history of hypotension. Before initiating Steglujan, volume status should be assessed and corrected if indicated. Monitor for signs and symptoms after initiating therapy.

Due to its mechanism of action, ertugliflozin induces an osmotic diuresis and increases serum creatinine and decreases eGFR. Increases in serum creatinine and decreases in eGFR were greater in patients with moderate renal impairment (see section 4.8).

In case of conditions that may lead to fluid loss (e.g., gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving Steglujan. Temporary interruption of treatment with Steglujan should be considered until the fluid loss is corrected.

Diabetic ketoacidosis
Rare cases of DKA, including life-threatening and fatal cases, have been reported in clinical trials and post-marketing in patients treated with sodium glucose co-transporter-2 (SGLT2) inhibitors, including ertugliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of ertugliflozin.

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

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

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of

blood ketone levels is preferred to urine. Treatment with Steglujan may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating Steglujan, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g., type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery, or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of Steglujan in patients with type 1 diabetes have not been established and Steglujan should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Lower limb amputations

In a long-term cardiovascular outcomes study VERTIS CV (eValuation of ERTugliflozin effIcacy and Safety, CardioVascular), a study in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, non-traumatic lower limb amputations (primarily of the toe) were reported with an incidence of 2.0% (0.57 subjects with event per 100 patient years), 2.1% (0.60 subjects with event per 100 patient years) and 1.6% (0.47 subjects with event per 100 patient years) for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups. The event rates of lower limb amputations were 0.75 and 0.96 versus 0.74 events per 100 patient years for ertugliflozin 5 mg and ertugliflozin 15 mg versus placebo, respectively. An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is not known whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Renal impairment

The efficacy of ertugliflozin for glycaemic control is dependent on renal function, and glycaemic efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2).

Steglujan should not be initiated in patients with an eGFR below 60 mL/min/1.73 m^2 or CrCl below 60 mL/min. Steglujan should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl is persistently below 45 mL/min due to a reduction of efficacy.

Monitoring of renal function is recommended as follows:

- Prior to Steglujan initiation and periodically during treatment (see section 4.2).
- More frequently in patients with an eGFR below 60 mL/min/1.73 m^2 or a CrCl below 60 mL/min.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function.

Hypoglycaemia with concomitant use with insulin and insulin secretagogues
Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue, which are known to cause hypoglycaemia (see section 4.8). Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimise the risk of hypoglycaemia when used in combination with Steglujan (see sections 4.2 and 4.5).

Genital mycotic infections
Ertugliflozin increases the risk of genital mycotic infections. In trials with SGLT2 inhibitors, patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections (see section 4.8). Patients should be monitored and treated appropriately.

Urinary tract infections
Urinary glucose excretion may be associated with an increased risk of urinary tract infections (see section 4.8). Temporary interruption of ertugliflozin should be considered when treating pyelonephritis or urosepsis.

Necrotising fasciitis of the perineum (Fournier's gangrene)
Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Steglujan should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Hypersensitivity reactions
Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported (see section 4.8). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, Steglujan should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated.

Severe and Disabling Arthralgia
There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous pemphigoid
There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, Steglujan should be discontinued.

Elderly patients
Elderly patients may be at an increased risk of volume depletion and renal impairment. Patients 65 years and older treated with ertugliflozin, had a higher incidence of adverse reactions related to volume depletion compared to younger patients. Steglujan is expected to have diminished efficacy in elderly patients with renal impairment (see sections 4.2 and 4.8).

Cardiac failure
Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with Steglujan in NYHA class III-IV.

Urine laboratory assessments
Due to the mechanism of action of ertugliflozin, patients taking Steglujan will test positive for glucose in their urine. Alternative methods should be used to monitor glycaemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) assay
Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Alternative methods should be used to monitor glycaemic control.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic drug interaction studies with Steglujan have not been performed; however, such studies have been conducted with ertugliflozin and sitagliptin, the individual active substances of Steglujan.

Ertugliflozin

Pharmacodynamic interactions

Diuretics
Ertugliflozin may add to the diuretic effect of diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Ertugliflozin may increase the risk of hypoglycaemia when used in combination with insulin and/or an insulin secretagogue. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with Steglujan (see sections 4.2, 4.4, and 4.8).

Pharmacokinetic interactions

Effects of other medicinal products on the pharmacokinetics of ertugliflozin
Metabolism by UGT1A9 and UGT2B7 is the primary clearance mechanism for ertugliflozin.

Interaction studies conducted in healthy subjects, using a single dose design, suggest that the pharmacokinetics of ertugliflozin are not altered by sitagliptin, metformin, glimepiride, or simvastatin.

Multiple-dose administration of rifampin (a UGT and CYP inducer) decreases ertugliflozin AUC and C_{max} by 39% and 15%, respectively. This decrease in exposure is not considered clinically relevant and therefore, no dose adjustment is recommended. A clinically relevant effect with other inducers (e.g., carbamazepine, phenytoin, phenobarbital) is not expected.

The impact of UGT inhibitors on the pharmacokinetics of ertugliflozin has not been studied clinically, but potential increase in ertugliflozin exposure due to UGT inhibition is not considered to be clinically relevant.

Effects of ertugliflozin on the pharmacokinetics of other medicinal products
Interaction studies conducted in healthy volunteers suggest that ertugliflozin had no clinically relevant effect on the pharmacokinetics of sitagliptin, metformin, and glimepiride.

Coadministration of simvastatin with ertugliflozin resulted in a 24% and 19% increase in AUC and C_{max} of simvastatin, respectively, and 30% and 16% increase in AUC and C_{max} of simvastatin acid,

respectively. The mechanism for the small increases in simvastatin and simvastatin acid is unknown and is not perpetrated through OATP inhibition by ertugliflozin. These increases are not considered to be clinically meaningful.

Sitagliptin
Pharmacokinetic interactions

Effects of other medicinal products on sitagliptin
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. *In vitro* studies indicate that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8.

Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD.
Interaction studies conducted in patients with type 2 diabetes or healthy volunteers suggest that metformin and ciclosporin had no clinically relevant effect on the pharmacokinetics of sitagliptin.

Effects of sitagliptin on other medicinal products
In drug interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives.

Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11% and the plasma C_{max} on average by 18%. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Steglujan in pregnant women. There are limited data from the use of ertugliflozin in pregnant women. Based on results from animal studies, ertugliflozin may affect renal development and maturation (see section 5.3). Therefore, Steglujan should not be used during pregnancy.

Breast-feeding
There is no information regarding the presence of Steglujan or its individual components in human milk, the effects on the breast-fed infant, or the effects on milk production. No studies in lactating animals have been conducted with the combined components of Steglujan. Ertugliflozin and sitagliptin are present in the milk of lactating rats. Ertugliflozin caused effects in the offspring of lactating rats.

Pharmacologically mediated effects were observed in juvenile rats treated with ertugliflozin (see section 5.3). Since human kidney maturation occurs *in utero* and during the first 2 years of life when exposure from breast-feeding may occur, a risk to newborns/infants cannot be excluded. Steglujan should not be used during breast-feeding.

Fertility
The effect of Steglujan on fertility in humans has not been studied. No effects of ertugliflozin or sitagliptin on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Steglujan has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been

reported with sitagliptin. In addition, patients should be alerted to the risk of hypoglycaemia when Steglujan is used in combination with insulin or an insulin secretagogue and to the elevated risk of adverse reactions related to volume depletion, such as postural dizziness (see sections 4.2, 4.4, and 4.8).

4.8 Undesirable effects

Summary of the safety profile

Ertugliflozin and sitagliptin
The safety of concomitantly administered ertugliflozin and sitagliptin has been evaluated in 990 patients with type 2 diabetes mellitus treated for 26 weeks in three studies; a factorial study of ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg once daily compared to the individual components, a placebo-controlled study of ertugliflozin 5 mg or 15 mg as add-on therapy to sitagliptin 100 mg and metformin once daily, and a placebo-controlled study of initial therapy with ertugliflozin 5 mg or 15 mg once daily in combination with sitagliptin 100 mg once daily (see section 5.1). The incidence and type of adverse reactions in these three studies were similar to the adverse reactions seen with ertugliflozin and are described below in Table 1. There were no additional adverse reactions identified in these three trials that included sitagliptin relative to the three placebo-controlled studies with ertugliflozin (see below).

Ertugliflozin
The safety and tolerability of ertugliflozin were assessed in 7 placebo- or active comparator-controlled studies with a total of 3,409 patients with type 2 diabetes mellitus treated with ertugliflozin 5 mg or 15 mg. In addition, the safety and tolerability of ertugliflozin in patients with type 2 diabetes and established atherosclerotic cardiovascular disease were assessed in VERTIS CV (see section 5.1) with a total of 5,493 patients treated with ertugliflozin 5 mg or 15 mg and a mean duration of exposure of 2.9 years.

Pool of placebo-controlled trials
The primary assessment of safety was conducted in a pool of three 26-week, placebo-controlled trials. Ertugliflozin was used as monotherapy in one trial and as add-on therapy in two trials (see section 5.1). These data reflect exposure of 1,029 patients to ertugliflozin with a mean exposure duration of approximately 25 weeks. Patients received ertugliflozin 5 mg (N=519), ertugliflozin 15 mg (N=510), or placebo (N=515) once daily.

The most commonly reported adverse reactions across the clinical program were vulvovaginal mycotic infection and other female genital mycotic infections. Serious diabetic ketoacidosis occurred rarely. See “Description of selected adverse reactions” for frequencies and see section 4.4.

Sitagliptin
Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (4.7%-13.8%) and insulin (9.6%) (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse reactions from placebo- and active comparator-controlled clinical trials and post-marketing experience

System Organ Class Frequency	**Adverse Reaction**
Infections and infestations	
Very common	Vulvovaginal mycotic infection and other female genital mycotic infections*,†,1 Urinary tract infections†,1
Common	Balanitis candida and other male genital mycotic infections*,†,1
Not known	Necrotising fasciitis of the perineum (Fournier's gangrene)*
Blood and lymphatic system disorders	
Rare	Thrombocytopenia2
Immune system disorders	
Not known	Hypersensitivity reactions including anaphylactic responses*,a,2
Metabolism and nutrition disorders	
Common	Hypoglycaemia*,†,1,2
Rare	Diabetic ketoacidosis*,†,1
Nervous system disorders	
Common Uncommon	Headache2 Dizziness2
Respiratory, thoracic and mediastinal disorders	
Not known	Interstitial lung disease[a,2]
Gastrointestinal disorders	
Uncommon Not known Not known Not known	Constipation2 Vomiting[a,2] Acute pancreatitis[a,*,b,2] Fatal and non-fatal haemorrhagic and necrotising pancreatitis *,a,2
Skin and subcutaneous tissue disorders	
Uncommon Not known Not known Not known Not known Not known Not known	Pruritus[a,2] Angioedema[a,*,2] Rash[a,*,2] Urticaria[a,*,2] Cutaneous vasculitis[a,*,2] Exfoliative skin conditions including Stevens-Johnson syndrome[a,*,2] Bullous pemphigoid[a,*,2]
Musculoskeletal and connective tissue disorders	
Not known Not known Not known Not known	Arthralgia[a,2] Myalgia[a,2] Back pain[a,2] Arthropathy[a,2]
Vascular disorders	
Common	Volume depletion*,†,1

Renal and urinary disorders	
Common Uncommon Not known Not known	Increased urination[‡,1] Dysuria[1], Blood creatinine increased/Glomerular filtration rate decreased[†,1] Impaired renal function[a,2] Acute renal failure[a,2]
Reproductive system and breast disorders	
Common	Vulvovaginal pruritus[1]
General disorders and administration site conditions	
Common	Thirst[§,1]
Investigations	
Common	Serum lipids changed[¶,1], Haemoglobin increased[**,1], BUN increased[¶¶,1]

[1] Adverse reaction with ertugliflozin.
[2] Adverse reaction with sitagliptin.
* See section 4.4.
† See subsections below for additional information.
‡ Includes: pollakiuria, micturition urgency, polyuria, urine output increased, and nocturia.
§ Includes: thirst and polydipsia.
¶ Mean percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were LDL-C 5.8% and 8.4% versus 3.2%; total cholesterol 2.8% and 5.7% versus 1.1%; however, HDL-C 6.2% and 7.6% versus 1.9%. Median percent changes from baseline for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were triglycerides -3.9% and -1.7% versus 4.5%.
** The proportion of subjects having at least 1 increase in haemoglobin > 2.0 g/dL was higher in the ertugliflozin 5 mg and 15 mg groups (4.7% and 4.1%, respectively) compared to the placebo group (0.6%).
¶¶ The proportion of subjects having any occurrence of BUN values ≥50% increase and value >ULN was numerically higher in the ertugliflozin 5 mg group and higher in the 15 mg group (7.9% and 9.8%, respectively) relative to the placebo group (5.1%).
[a] Adverse reactions were identified through post-marketing surveillance.
[b] See *Sitagliptin cardiovascular outcomes study (TECOS)* below.

Description of selected adverse reactions

Volume depletion (ertugliflozin)
Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of placebo-controlled studies, the incidence of adverse events related to volume depletion (dehydration, dizziness postural, presyncope, syncope, hypotension and orthostatic hypotension) was low (< 2%) and not notably different across the ertugliflozin and placebo groups. In the subgroup analyses in the broader pool of Phase 3 studies, subjects with eGFR < 60 mL/min/1.73 m^2, subjects ≥ 65 years of age and subjects on diuretics had a higher incidence of volume depletion in the ertugliflozin groups relative to the comparator group (see sections 4.2 and 4.4). In subjects with eGFR < 60 mL/min/1.73 m^2, the incidence was 5.1%, 2.6% and 0.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and the comparator group and for subjects with eGFR 45 to < 60 mL/min/1.73 m^2, the incidence was 6.4%, 3.7% and 0% respectively.

Hypoglycaemia (ertugliflozin)
In the pool of placebo-controlled studies, the incidence of documented hypoglycaemia was increased for ertugliflozin 5 mg and 15 mg (5.0% and 4.5%) compared to placebo (2.9%). In this population, the incidence of severe hypoglycaemia was 0.4% in each group. When ertugliflozin was used as monotherapy, the incidence of hypoglycaemic events in the ertugliflozin groups was 2.6% in both groups and 0.7% in the placebo group. When used as add-on to metformin, the incidence of hypoglycaemic events was 7.2% in the ertugliflozin 5 mg group, 7.8% in the ertugliflozin 15 mg group and 4.3% in the placebo group.

When ertugliflozin was added to metformin and compared to sulphonylurea, the incidence of hypoglycaemia was higher for the sulphonylurea (27%) compared to ertugliflozin (5.6% and 8.2% for ertugliflozin 5 mg and 15 mg, respectively).

In the VERTIS CV sub-studies, when ertugliflozin was added to insulin with or without metformin, the incidences of documented hypoglycaemia were 39.4%, 38.9% and 37.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to a sulphonylurea, the incidences of hypoglycaemia were 7.3%, 9.3% and 4.2% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to metformin and a sulphonylurea, the incidences of hypoglycaemia were 20.0%, 26.5% and 14.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

In patients with moderate renal impairment taking insulins, sulphonylurea, or meglitinides as background medication, documented hypoglycaemia was 36%, 27% and 36% for ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively (see sections 4.2, 4.4, and 4.5).

Diabetic ketoacidosis (ertugliflozin)
In VERTIS CV, ketoacidosis was identified in 19 (0.3%) ertugliflozin-treated patients and in 2 (0.1%) placebo-treated patients. Across 7 other Phase 3 clinical trials in the ertugliflozin development program, ketoacidosis was identified in 3 (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients (see section 4.4).

Blood creatinine increased/Glomerular filtration rate decreased and renal-related events (ertugliflozin)
Initial increases in mean creatinine and decreases in mean eGFR in patients treated with ertugliflozin were generally transient during continuous treatment. Patients with moderate renal impairment at baseline had larger mean changes that did not return to baseline at Week 26; these changes reversed after treatment discontinuation.

Renal-related adverse reactions (e.g., acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with ertugliflozin, particularly in patients with moderate renal impairment where the incidence of renal-related adverse reactions was 2.5%, 1.3%, and 0.6% in patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively.

Genital mycotic infections (ertugliflozin)
In the pool of three placebo-controlled clinical trials, female genital mycotic infections (e.g., genital candidiasis, genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis) occurred in 9.1%, 12%, and 3.0% of females treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. In females, discontinuation due to genital mycotic infections occurred in 0.6% and 0% of patients treated with ertugliflozin and placebo, respectively (see section 4.4).

In the same pool, male genital mycotic infections (e.g., balanitis candida, balanoposthitis, genital infection, genital infection fungal) occurred in 3.7%, 4.2%, and 0.4% of males treated with ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males. In males, discontinuations due to genital mycotic infections occurred in 0.2% and 0% of patients treated with ertugliflozin and placebo, respectively. In rare instances, phimosis was reported and sometimes circumcision was performed (see section 4.4).

Urinary tract infections (ertugliflozin)
In VERTIS CV, urinary tract infections occurred in 12.2%, 12.0% and 10.2% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. The incidences of serious urinary tract infections were 0.9%, 0.4%, and 0.8% with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

Across 7 other Phase 3 clinical trials in the ertugliflozin development program, the incidences of urinary tract infections were 4.0% and 4.1% for ertugliflozin 5 mg and 15 mg groups and 3.9% for placebo. Most of the events were mild or moderate, and no serious cases were reported.

Sitagliptin
In addition to the adverse reactions described in the table above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5% and more commonly in patients treated with sitagliptin included upper respiratory tract infection and nasopharyngitis. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with sitagliptin (not reaching the 5% level, but occurring with an incidence of > 0.5% higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other anti-diabetic medicinal products than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequency very common with the combination of sulphonylurea and metformin), influenza (common with insulin (with or without metformin)), nausea and vomiting (common with metformin), flatulence (common with metformin or pioglitazone), constipation (common with the combination of sulphonylurea and metformin), peripheral oedema (common with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (uncommon with metformin), and dry mouth (uncommon with insulin (with or without metformin)).

TECOS (trial evaluating cardiovascular outcomes with sitagliptin)
The cardiovascular safety study with sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA1c and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulphonylurea at baseline, the incidence of severe hypoglycaemia was 2.7% in sitagliptin-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulphonylurea at baseline, the incidence of severe hypoglycaemia was 1.0% in sitagliptin-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients.

Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of sitagliptin as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Mouth ulceration; stomatitis; rhabdomyolysis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to the Ministry of Health according to the National Regulation by using an online form
/https://sideeffects.health.gov.il

4.9 Overdose

In the event of an overdose with Steglujan, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring including obtaining an electrocardiogram, and institute supportive treatment) as dictated by the patient's clinical status.

Ertugliflozin
Ertugliflozin did not show any toxicity in healthy subjects at single oral doses up to 300 mg and multiple doses up to 100 mg daily for 2 weeks. No potential acute symptoms and signs of overdose were identified. Removal of ertugliflozin by haemodialysis has not been studied.

Sitagliptin
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase 1 multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD24.

Mechanism of action
Steglujan combines two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: ertugliflozin, a SGLT2 inhibitor, and sitagliptin phosphate, a DPP-4 inhibitor.

Ertugliflozin
SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Ertugliflozin is a potent, selective, and reversible inhibitor of SGLT2. By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Sitagliptin
Sitagliptin is a member of a class of oral antihyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this medicinal product may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases

glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A_{1c} (HbA_{1c}) and lower fasting and post-prandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Pharmacodynamic effects

Ertugliflozin

Urinary glucose excretion and urinary volume
Dose-dependent increases in the amount of glucose excreted in urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following single- and multiple-dose administration of ertugliflozin. Dose-response modelling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (UGE) in patients with type 2 diabetes mellitus, providing 87% and 96% of maximal inhibition, respectively.

Clinical efficacy and safety

Ertugliflozin in combination with sitagliptin
The efficacy and safety of ertugliflozin in combination with sitagliptin have been studied in 3 multi-centre, randomised, double-blind, placebo- and active comparator-controlled, Phase 3 clinical studies involving 1,985 patients with type 2 diabetes. Across the 3 studies, the racial distribution ranged from 72.9% to 90.4% White, 0.0% to 20.3% Asian, 1.9% to 4.5% Black and 4.8% to 5.4% Other. Hispanic or Latino patients comprised 15.6% to 36.1% of the population. The mean age of the patients across these 3 studies ranged from 55.1 to 59.1 years (range 21 years to 85 years). Across the 3 studies, 16.2% to 29.9% of patients were ≥ 65 years of age and 2.3% to 2.8% were ≥ 75 years of age.

Factorial study with ertugliflozin and sitagliptin as add-on combination therapy with metformin
A total of 1,233 patients with type 2 diabetes participated in a randomised, double-blind, multi-centre, 26-week, active-controlled study to evaluate the efficacy and safety of ertugliflozin 5 mg or 15 mg in combination with sitagliptin 100 mg compared to the individual components. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥ 1,500 mg/day) were randomised to one of five active-treatment arms: ertugliflozin 5 mg or 15 mg, sitagliptin 100 mg, or sitagliptin 100 mg in combination with 5 mg or 15 mg ertugliflozin administered once daily in addition to continuation of background metformin therapy (see Table 2).

Table 2: Results at Week 26 from a factorial study with ertugliflozin and sitagliptin as add-on combination therapy with metformin compared to individual components alone*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Sitagliptin 100 mg	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg
HbA1c (%)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	8.6	8.6	8.5	8.6	8.6
Change from baseline (LS mean†)	-1.0	-1.1	-1.1	-1.5	-1.5
Difference from Sitagliptin				-0.4‡ (-0.6, -0.3)	-0.5‡ (-0.6, -0.3)
Difference from Ertugliflozin 5 mg				-0.5‡ (-0.6, -0.3)	
Difference from Ertugliflozin 15 mg					-0.4‡ (-0.6, -0.3)
(LS mean†, 95% CI)					
Patients [N (%)] with HbA1c < 7%	66 (26.4)	79 (31.9)	81 (32.8)	127§ (52.3)	120§ (49.2)
Body weight (kg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	88.6	88.0	89.8	89.5	87.5
Change from baseline (LS mean†)	-2.7	-3.7	-0.7	-2.5	-2.9
Difference from Sitagliptin (LS mean†, 95% CI)				-1.8‡ (-2.5, -1.2)	-2.3‡ (-2.9, -1.6)

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, baseline eGFR and the interaction of time by treatment.
‡ p< 0.001 compared to control group.
§ p< 0.001 compared to corresponding dose of ertugliflozin or sitagliptin (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Ertugliflozin as add-on combination therapy with metformin and sitagliptin

A total of 463 patients, with type 2 diabetes inadequately controlled on metformin (≥ 1,500 mg/day) and sitagliptin 100 mg once daily participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of ertugliflozin. Patients were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo administered once daily in addition to continuation of background metformin and sitagliptin therapy (see Table 3).

Table 3: Results at Week 26 from an add-on study of ertugliflozin in combination with metformin and sitagliptin*

	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
HbA1c (%)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	8.1	8.0	8.0
Change from baseline (LS mean†)	-0.8	-0.9	-0.1
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.9, -0.5)	-0.8‡ (-0.9, -0.6)	
Patients [N (%)] with HbA1c < 7%	50 (32.1)§	61 (39.9)§	26 (17.0)
Body Weight (kg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.3	-3.0	-1.3
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-2.6, -1.4)	-1.7‡ (-2.3, -1.1)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, prior antihyperglycaemic medication, baseline eGFR, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Combination therapy of ertugliflozin and sitagliptin
A total of 291 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a randomised, double-blind, multi-centre, placebo-controlled 26-week study to evaluate the efficacy and safety of ertugliflozin in combination with sitagliptin. These patients, who were not receiving any background antihyperglycaemic treatment, were randomised to ertugliflozin 5 mg or ertugliflozin 15 mg in combination with sitagliptin (100 mg) or to placebo, once daily (see Table 4).

Table 4: Results at Week-26 from a combination therapy study of ertugliflozin and sitagliptin*

	Ertugliflozin 5 mg + Sitagliptin	**Ertugliflozin 15 mg + Sitagliptin**	**Placebo**
HbA1c (%)	**N = 98**	**N = 96**	**N = 96**
Baseline (mean)	8.9	9.0	9.0
Change from baseline (LS mean†)	-1.6	-1.7	-0.4
Difference from placebo (LS mean† and 95% CI)	-1.2‡ (-1.5, -0.8)	-1.2‡ (-1.6, -0.9)	
Patients [N (%)] with HbA1c < 7%	35 (35.7)§	30 (31.3)§	8 (8.3)
Body Weight (kg)	**N = 98**	**N = 96**	**N = 97**
Baseline (mean)	90.8	91.3	95.0
Change from baseline (LS mean†)	-2.9	-3.0	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-3.0, -1.0)	-2.1‡ (-3.1, -1.1)	

* N includes all patients who received at least one dose of study medication and had at least one measurement of the outcome variable.
† Least squares means adjusted for time, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Fasting plasma glucose
In three placebo-controlled studies, ertugliflozin resulted in statistically significant reductions in FPG. For ertugliflozin 5 mg and 15 mg, respectively, the placebo-corrected reductions in FPG were 1.92 and 2.44 mmol/L as monotherapy, 1.48 and 2.12 mmol/L as add-on to metformin, and 1.40 and 1.74 mmol/L as add-on to metformin and sitagliptin.

The combination of ertugliflozin and sitagliptin resulted in significantly greater reductions in FPG compared to sitagliptin or ertugliflozin alone or placebo. The combination of ertugliflozin 5 or 15 mg and sitagliptin resulted in incremental FPG reductions of 0.46 to 0.65 mmol/L compared to the ertugliflozin alone or 1.02 to 1.28 mmol/L compared to sitagliptin alone. The placebo-corrected reductions of ertugliflozin 5 or 15 mg in combination with sitagliptin were 2.16 and 2.56 mmol/L.

Efficacy in patients with baseline HbA1c ≥ 10%
In the study of patients inadequately controlled on metformin with baseline HbA1c from 7.5-11.0%, among the subgroup of patients with a baseline HbA1c ≥ 10%, the combination of ertugliflozin 5 mg or 15 mg with sitagliptin resulted in reductions of HbA1c of 2.35% and 2.66%, respectively, compared to 2.10%, 1.30%, and 1.82% for ertugliflozin 5 mg, ertugliflozin 15 mg, and sitagliptin alone, respectively.

Post-prandial glucose
When used in monotherapy, ertugliflozin 5 and 15 mg resulted in statistically significant placebo-corrected reductions in 2-hour post-prandial glucose (PPG) of 3.83 and 3.74 mmol/L.

The combination of ertugliflozin 5 or 15 mg with sitagliptin resulted in statistically significant placebo-corrected reductions in 2-hour PPG of 3.46 and 3.87 mmol/L.

Blood pressure
After 26-weeks of treatment, the combination of ertugliflozin 5 mg or 15 mg and sitagliptin 100 mg resulted in statistically significant reductions in systolic blood pressure (SBP) compared to sitagliptin alone (-2.8 and -3.0 mmHg for E5/S100 and E15/S100 respectively) or placebo (-4.4 and -6.4 mmHg

for E5/S100 and E15/S100, respectively). Additionally, when added on to background metformin and sitagliptin therapy, ertugliflozin 5 mg and 15 mg resulted in statistically significant placebo subtracted reductions in SBP of 2.9 and 3.9 mmHg, respectively.

Subgroup analysis
In patients with type 2 diabetes treated with ertugliflozin in combination with sitagliptin, the improvement in HbA1c was similar across subgroups defined by age, sex, and race, and duration of type 2 diabetes mellitus.

Sitagliptin cardiovascular outcomes study (TECOS)
The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an $HbA1_c$ of ≥ 6.5 to 8.0% with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the sitagliptin and placebo groups was 0.29% (0.01), 95% CI (-0.32, -0.27); p< 0.001. The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (see Table 5).

Table 5: Rates of composite cardiovascular outcomes and key secondary outcomes

	Sitagliptin 100 mg		Placebo			
	N (%)	Incidence rate per 100 patient-years*	N (%)	Incidence rate per 100 patient-years*	Hazard Ratio (95% CI)	p-value†
Analysis in the Intention-to-Treat Population						
Number of patients	7,332		7,339			
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89–1.08)	< 0.001
Secondary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	< 0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalisation for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalisation for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

*Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).

† Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

‡The analysis of hospitalisation for heart failure was adjusted for a history of heart failure at baseline.

5.2 Pharmacokinetic properties

Steglujan

Steglujan has been shown to be bioequivalent to coadministration of corresponding doses of ertugliflozin and sitagliptin tablets.

The effects of a high-fat meal on the pharmacokinetics of ertugliflozin and sitagliptin when administered as Steglujan tablets are comparable to those reported for the individual tablets. Administration of Steglujan with food decreased ertugliflozin C_{max} by 29% and had no meaningful effect on ertugliflozin AUC_{inf}, or on sitagliptin AUC_{inf} and C_{max}.

Ertugliflozin

General introduction

The pharmacokinetics of ertugliflozin are similar in healthy subjects and patients with type 2 diabetes. The steady state mean plasma AUC and C_{max} were 398 ng·hr/mL and 81 ng/mL, respectively, with 5 mg ertugliflozin once daily treatment, and 1,193 ng·hr/mL and 268 ng/mL, respectively, with 15 mg

ertugliflozin once daily treatment. Steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin. Ertugliflozin does not exhibit time-dependent pharmacokinetics and accumulates in plasma up to 10-40% following multiple dosing.

Absorption
Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, peak plasma concentrations (median T_{max}) of ertugliflozin occur at 1 hour post-dose under fasted conditions. Plasma C_{max} and AUC of ertugliflozin increase in a dose-proportional manner following single doses from 0.5 mg to 300 mg and following multiple doses from 1 mg to 100 mg. The absolute oral bioavailability of ertugliflozin following administration of a 15-mg dose is approximately 100%.

Administration of ertugliflozin with a high-fat and high-calorie meal decreases ertugliflozin C_{max} by 29% and prolongs T_{max} by 1 hour but does not alter AUC as compared with the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered with or without food. In Phase 3 clinical trials, ertugliflozin was administered without regard to meals.

Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters.

Distribution
The mean steady-state volume of distribution of ertugliflozin following an intravenous dose is 86 l. Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.

Ertugliflozin is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3) *in vitro.*

Biotransformation
Metabolism is the primary clearance mechanism for ertugliflozin. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation to two glucuronides that are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%).

Elimination
The mean systemic plasma clearance following an intravenous 100 µg dose was 11 l/hr. The mean elimination half-life in type 2 diabetic patients with normal renal function was estimated to be 17 hours based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 41% and 50% of the drug-related radioactivity was eliminated in faeces and urine, respectively. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 34% as unchanged ertugliflozin in faeces, which is likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.

Special populations

Renal impairment
In a Phase 1 clinical pharmacology study in patients with type 2 diabetes and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg ertugliflozin, the mean increases in AUC of ertugliflozin were ≤ 1.7-fold, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically relevant. There were no clinically meaningful differences in the ertugliflozin C_{max} values among the different renal function groups. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment (see section 4.4). The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

Hepatic impairment
Moderate hepatic impairment (based on the Child-Pugh classification) did not result in an increase in exposure of ertugliflozin. The AUC of ertugliflozin decreased by approximately 13%, and C_{max} decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.

Paediatric population
No studies with ertugliflozin have been performed in paediatric patients.

Effects of age, body weight, gender and race
Based on a population pharmacokinetic analysis, age, body weight, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin.

Sitagliptin

Absorption
Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Mean plasma AUC of sitagliptin was 8.52 μM•hr and C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87%. Since coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, Steglujan may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 l. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Biotransformation
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
Following administration of an oral [^{14}C]-sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of P-gp, which may also be involved in mediating the

renal elimination of sitagliptin. However, ciclosporin, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or peptide transporter 1/2 (PEPT1/2) transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC_{50}=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of P-gp.

Drug interactions
No drug interactions studies have been performed with Steglujan and other medicinal products; however, such studies have been conducted with the individual active substances.

In vitro assessment of ertugliflozin
In *in vitro* studies, ertugliflozin and ertugliflozin glucuronides did not inhibit or inactivate CYPs 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin and ertugliflozin glucuronides did not inhibit the activity of UGTs 1A6, 1A9 or 2B7 *in vitro*. Ertugliflozin was a weak inhibitor of UGTs 1A1 and 1A4 *in vitro* at higher concentrations that are not clinically relevant. Ertugliflozin glucuronides had no effect on these isoforms. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered drugs eliminated by these enzymes.

Ertugliflozin or ertugliflozin glucuronides do not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 transporters or transporting polypeptides OATP1B1 and OATP1B3 at clinically relevant concentrations *in vitro*. Overall, ertugliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are substrates of these transporters.

In vitro assessment of sitagliptin
In vitro data suggest that sitagliptin does not inhibit or induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and OCT. Sitagliptin may be a mild inhibitor of P-gp *in vivo*.

In vitro transport studies showed that sitagliptin is a substrate for P-gp and OAT3. OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

Characteristics in patients
The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment
In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD).

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased modestly in patients with GFR ≥ 45 to < 90 mL/min. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Hepatic impairment
No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly
No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase 1 and Phase 2 data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric
No studies with sitagliptin have been performed in paediatric patients.

Other patient characteristics
No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase 1 pharmacokinetic data and on a population pharmacokinetic analysis of Phase 1 and Phase 2 data.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute toxicity, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Ertugliflozin

General toxicity
Repeat-dose oral toxicity studies were conducted in mice, rats, and dogs for up to 13, 26, and 39 weeks, respectively. Signs of toxicity that were considered adverse were generally observed at exposures greater than or equal to 77 times the human unbound exposure (AUC) at the maximum recommended human dose (MRHD) of 15 mg/day. Most toxicity was consistent with pharmacology related to urinary glucose loss and included decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism, gluconeogenesis and electrolyte imbalances, and urinary changes such as polyuria, glucosuria, and calciuria. Microscopic changes related to glucosuria and/or calciuria observed only in rodents included dilatation of renal tubules, hypertrophy of zona glomerulosa in adrenal glands (rats), and increased trabecular bone (rats). Except for emesis, there were no adverse toxicity findings in dogs at 379 times the human unbound exposure (AUC) at the MRHD of 15 mg/day.

Carcinogenesis
In the 2-year mouse carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 5, 15, and 40 mg/kg/day. There were no ertugliflozin-related neoplastic findings at doses up to 40 mg/kg/day (approximately 41 times human unbound exposure at the MRHD of 15 mg/day based on AUC). In the 2-year rat carcinogenicity study, ertugliflozin was administered by oral gavage at doses of 1.5, 5, and 15 mg/kg/day. Ertugliflozin-related neoplastic findings included an increased incidence of benign adrenal medullary pheochromocytoma in male rats at 15 mg/kg/day. This finding was attributed to carbohydrate malabsorption leading to altered calcium homeostasis and was not considered relevant to human risk. The no-observed-effect level (NOEL) for neoplasia was 5 mg/kg/day (approximately 16 times human unbound exposure at the MRHD of 15 mg/day).

Mutagenesis
Ertugliflozin was not mutagenic or clastogenic with or without metabolic activation in the microbial reverse mutation, *in vitro* cytogenetic (human lymphocytes), and *in vivo* rat micronucleus assays.

Reproductive toxicology
In the rat fertility and embryonic development study, male and female rats were administered ertugliflozin at 5, 25, and 250 mg/kg/day. No effects on fertility were observed at 250 mg/kg/day (approximately 386 times human unbound exposure at the MRHD of 15 mg/day based on AUC comparisons). Ertugliflozin did not adversely affect developmental outcomes in rats and rabbits at maternal exposures that were 239 and 1,069 times, respectively, the human exposure at the maximum

clinical dose of 15 mg/day, based on AUC. At a maternally toxic dose in rats (250 mg/kg/day), lower foetal viability and a higher incidence of a visceral malformation were observed at maternal exposure that was 510 times the maximum clinical dose of 15 mg/day.

In the pre- and post-natal development study, decreased post-natal growth and development were observed in rats administered ertugliflozin gestation day 6 through lactation day 21 at ≥ 100 mg/kg/day (estimated 239 times the human exposure at the maximum clinical dose of 15 mg/day, based on AUC). Sexual maturation was delayed in both sexes at 250 mg/kg/day (estimated 620 times the MRHD at 15 mg/day, based on AUC).

When ertugliflozin was administered to juvenile rats from post-natal day (PND) 21 to PND 90, a period of renal development corresponding to the late second and third trimesters of human pregnancy, increased kidney weights, dilatation of the renal pelvis and tubules, and renal tubular mineralisation were seen at an exposure 13 times the maximum clinical dose of 15 mg/day, based on AUC. Effects on bone (shorter femur length, increased trabecular bone in the femur) as well as effects of delayed puberty were observed at an exposure 817 times the MRHD of 15 mg/day based on AUC. The effects on kidney and bone did not fully reverse after the 1 month recovery period.

Sitagliptin

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No adverse effects upon fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460)
Calcium hydrogen phosphate (anhydrous)
Sodium stearyl fumarate (E487)
Croscarmellose sodium
Magnesium stearate (E470b)

Tablet coat
Hypromellose (E464)
Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)
Carnauba wax (E903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30^0C in the original package in order to protect from moisture.

6.5 Nature and contents of container

Alu/PVC/PA/Alu blisters
Packs of 14, 28, 30, 84, 90 and 98 film-coated tablets in non-perforated blisters.
Packs of 30x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O. Box 7121, Petah-Tikva 49170.

8. MANUFACTURER

Merck Sharp & Dohme Corp., New Jersey, USA

9. REGISTRATION NUMBERS

Steglujan 5 /100 mg tablets: 167-01-36006
Steglujan 15/100 mg tablets: 167-02-36036

Revised in February 2022 according to MOHs guidelines.