UNLEASH THE POWER WITHIN

Safety summary and prespecified adverse events (AEs)

Prespecified AEs at week 26 (ER)	E15 (n=248)	S100 (n=247)	E15/S100 (n=244)
Genital mycotic infection (female)	8 (7.0%)	1 (1.1%)	9 (7.6%)[a]
Genital mycotic infection (male)	5 (3.7%)	0	3 (2.4%)
Urinary tract infection	14 (5.6%)	8 (3.2%)	9 (3.7%)
Symptomatic hypoglycaemia[b]	6 (2.4%)	6 (2.4%)	12 (4.9%)[#]
Hypovolaemia	2 (0.8%)	0	0

Abbreviations: AE, adverse event; E5, ertugliflozin 5 mg; E15, ertugliflozin 15 mg; ER, analysis excludes events occurring after rescue medication; S100, sitagliptin 100 mg.
[a] *P*< .05 vs S100. [b] Event with clinical symptoms reported by the investigator as hypoglycaemia (biochemical documentation not required).

Steglujan Selected Safety Information

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, please refer to the full prescribing information.**

Contraindications:
Hypersensitivity to the active substances or to any of the excipients

Precautions:
- 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.
- Hypotension/Volume depletion : Ertugliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction. Therefore, symptomatic hypotension may occur after initiating Steglujan, particularly in patients with impaired renal function, elderly patients, patient 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. Be cautious if patients show signs of increase in serum creatinine and decrease in eGFR. Patient's volume status should be carefully monitored.
- Diabetic ketoacidosis (DKA) : 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, and cases have been reported in clinical trials with 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. Before initiating Steglujan, factors in the patient history that may predispose to ketoacidosis should be considered.
- Lower limb amputations : An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect.
  Like for all diabetic patients it is important to counsel patients on routine preventative foot care.
- Impairment in renal function : The efficacy of ertugliflozin is dependent on renal function. Steglujan should not be initiated in patients with an eGFR below 60 ml/min/1.73 m² or CrCl below 60 ml/min. Steglujan should be discontinued when eGFR is persistently below 45 ml/min/1.73 m² or CrCl is persistently below 45 ml/min due to a reduction of efficacy.
- 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. Lower dose of insulin or insulin secretagogue may be required to minimise the risk of hypoglycaemia when used in combination with Steglujan.
- 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. Patients should be monitored and treated appropriately.
- Urinary tract infections : Urinary glucose excretion may be associated with an increased risk of urinary tract infections. Temporary interruption of ertugliflozin should be considered when treating pyelonephritis or urosepsis.
- Hypersensitivity reactions : Hypersensitivity reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. 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.
- Bullous pemphigoid : If bullous pemphigoid is suspected, Steglujan should be discontinued.
- Elderly patients : Elderly patients may be at an increased risk of volume depletion. 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
- 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 : 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.

Adverse Events
- Very common and common side effects include vulvovaginal mycotic infection and other female genital mycotic infections, balanitis candida and other male genital mycotic infections, hypoglycaemia, headache, volume depletion, increased urination, vulvovaginal pruritus, thirst, serum lipids changed, haemoglobin increased, BUN increased.
- For detailed side effects, please refer to the full prescribing information.

Before prescribing, please consult the full prescribing information

References:
1. Hong Kong Product Insert (STEGLUJAN, MSD).
2. Pratley, R.E. *et al. Diabetes Obes Metab.* 2018;20:1111–1120.
3. Scheen, A.J., Expert Opinion On *Drug Metabolism & Toxicology*, 2016; 12(12): 1407–1417.
4. Pratley, R.E. *et al.* [supplemental appendix]. *Diabetes Obes Metab.* 2018;20:1111–1120. Available at: https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.13194. Accessed On 19 Mar 2020.
5. Fediuk, D. *et al.* Poster 1222-P. Presented at the American Diabetes Association 79th Scientific Sessions (ADA 2019), San Francisco, California. June 7-11, 2019.

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Steglujan™
(ertugliflozin and sitagliptin)

HK-LUJ-00002 03/20

For adults with type 2 diabetes, as an adjunct to diet and exercise, to improve glycemic control [1]

EXPERIENCE THE POWER OF STEGLUJAN

POWER in a single pill with convenient, once-daily dosing[1]

Steglujan™
(ertugliflozin and sitagliptin)

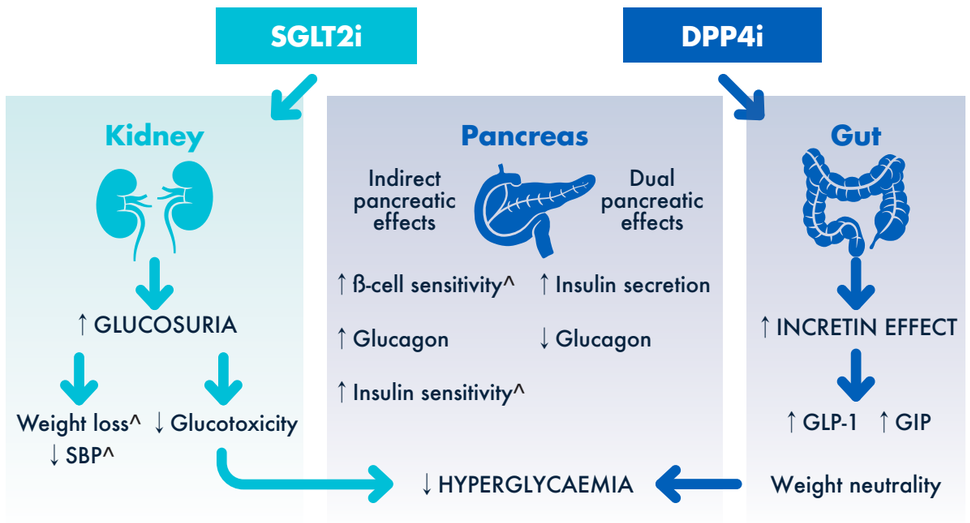
Steglujan™
(ertugliflozin and sitagliptin)

Steglujan, a fixed-dose combination containing Steglatro and Januvia, is your choice of oral anti-diabetic agent in helping your patient back to T2D control.[1]

- Offers **strong efficacy**[2*]
- Exert glucose-lowering effects via different and **complementary mechanisms**[3]
- **HOMA-β increased** relative to baseline in all groups[2^]
- Improves patients' treatment **adherence**[3]
- **Symptomatic hypoglycemia** was infrequent with Ertugliflozin 15mg /Sitagliptin 100mg[2#]

*Compare to the individual agents (ertugliflozin and sitagliptin)

A complementary approach to treat T2D with combination therapy[3]



A complementary pharmacological mechanism of action adapted from Scheen, A.J.[3]. For the indication and efficacy of Steglujan, please refer to the full prescribing information.

T2D, type 2 diabetes; SGLT2i, sodium-glucose cotransporter 2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; SBP, systolic blood pressure; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide

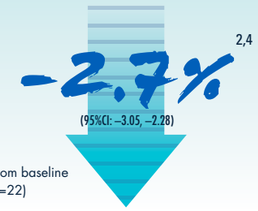
^Steglujan is not indicated for weight loss, reduction in SBP, increased beta-cell sensitivity or increased insulin sensitivity.

Vertis factorial: Primary end point

Change from baseline in HbA_{1c} at week 26

At Week 26, least squares mean HbA_{1c} reductions from baseline were greater with Ertugliflozin 5mg/Sitagliptin 100mg+ (-1.5%, 95% CI: -1.6, -1.4) and Ertugliflozin 15mg/Sitagliptin 100mg (–1.5%, 95% CI: -1.6, -1.4) than with individual agents (-1.0% (95%CI: -1.1, -0.9), -1.1 % (95%CI: -1.2, -1.0) and -1.1% (95%CI: -1.2, -0.9) for Ertugliflozin 5mg, Ertugliflozin 15mg and Sitagliptin 100mg, respectively; *P*<0.001 for all comparisons)

In patients with baseline HbA_{1c} ≥10%, Ertugliflozin 15mg + Sitagliptin 100mg led to **significantly greater reductions** from baseline HbA_{1c} at Week 26.



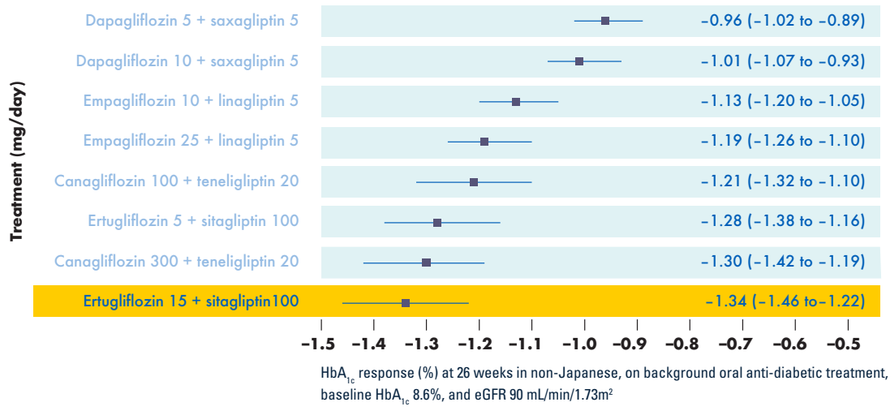
VERTIS Factorial was a 52-week, double-blind, multicentre, randomized, parallel-group study To evaluate the efficacy and safety of ertugliflozin and sitagliptin co-administration vs the individual agents in patients with type 2 diabetes who are inadequately controlled with metformin. 1233 patients aged ≥ 18 years old with type 2 diabetes on stable metformin ≥1500 mg/ d were enrolled. Patients with glycated haemoglobin (HbA_{1c}) ≥7.5% and ≤11.0% (≥58 and ≤97mmol/mol) with metformin ≥1500mg/d (n=1233) were randomized to ertugliflozin 5 (E5) or 15 (E15) mg/d, sitagliptin 100mg /d (S100) or to co- administration of E5/S100 or E15/S100. The primary endpoint was the change in HbA_{1c} from baseline to Week 26[2].

+Ertugliflozin 5mg/Sitagliptin 100mg is not available in Hong Kong.

Comparative efficacy of ertugliflozin vs other sodium-glucose cotransporter 2 inhibitors:

Model-based meta-analysis of HbA_{1c} lowering

Predicted HbA_{1c} response (placebo-adjusted mean change from baseline) with 95% CI at 26 weeks ranked by treatment effect for SGLT2i + DPP4i[5]



HbA_{1c} response (%) at 26 weeks in non-Japanese, on background oral anti-diabetic treatment, baseline HbA_{1c} 8.6%, and eGFR 90 mL/min/1.73m²

Figure shows SGLT2i + DPP4i with the most data available across various covariate categories.

CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; SGLT2i, sodium-glucose cotransporter 2 inhibitors.

Model-based meta-analysis: Summary-level data from the Quantify Diabetes Clinical Database and all randomized placebo- and active-controlled trials of ≤54 weeks duration in patients with T2DM were included. Trials evaluated the safety and efficacy of SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, tofogliflozin) and DPP4i (alogliptin, anagliptin, dutogliptin, gemigliptin, linagliptin, omarigliptin, retagliptin, saxagliptin, sitagliptin, teneligliptin, trelagliptin, vildagliptin)[5]