NEW DRUGS

Aust Prescr 2019;42:70–2
https://doi.org/10.18773/austprescr.2019.018
First published 28 February 2019

Corrected 26 April 2019
This is the corrected version of the article.
Correction notice available at: https://doi.org/10.18773/austprescr.2019.036

Ertugliflozin

Approved indication: type 2 diabetes

Steglatro (Merck Sharp & Dohme)
5 mg or 15 mg film-coated tablets

Segluromet (Merck Sharp & Dohme)
2.5 mg ertugliflozin/500 mg metformin,
2.5 mg ertugliflozin/1000 mg metformin,
7.5 mg ertugliflozin/500 mg metformin,
7.5 mg ertugliflozin/1000 mg metformin

Steglujan (Merck Sharp & Dohme)
5 mg ertugliflozin/100 mg sitagliptin,
15 mg ertugliflozin/100 mg sitagliptin

Australian Medicines Handbook section 10.1.5, Sodium-glucose co-transporter 2 inhibitors

Ertugliflozin is another sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated for type 2 diabetes. It can be used as a monotherapy (as an alternative when metformin is not appropriate) or in combination with other drugs for diabetes, in conjunction with diet and exercise.

Like other SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin, ertugliflozin reduces blood glucose by decreasing the renal reabsorption of glucose and increasing its excretion. Because glucose is lost in the urine, these drugs are also associated with weight loss.

The approval of ertugliflozin is based on seven randomised placebo or active comparator phase III trials (see Table).[1-8] In total, 4863 adults (mean age 58 years) with inadequately controlled type 2 diabetes were included. The main outcome in the trials was change in glycated haemoglobin (HbA1c). Body weight was also measured.

In a monotherapy trial (VERTIS MONO), patients were randomised to daily ertugliflozin (5 mg or 15 mg) or placebo. After 26 weeks of treatment, mean HbA1c had dropped with ertugliflozin but increased with placebo. This difference was statistically significant (p=0.001).[1] These lower HbA1c concentrations were maintained through to 52 weeks with ertugliflozin.[2] Decreases in HbA1c were also seen in a second trial (VERTIS SITA) in which ertugliflozin (5 mg or 15 mg) was given as initial therapy in combination with sitagliptin 100 mg (see Table).[3]

Reduction in HbA1c was observed when ertugliflozin was added to the treatment of patients whose blood glucose was inadequately controlled with metformin (VERTIS MET[4] and VERTIS SU[5] trials). In the VERTUS SU trial, adding ertugliflozin 15 mg was found to be non-inferior to adding glimepiride.[5]

In the VERTIS FACTORIAL trial HbA1c reductions were observed when ertugliflozin and sitagliptin were added to metformin.[6] Similar results were observed in the VERTIS SITA2 trial when ertugliflozin was given to patients already taking a combination of metformin and sitagliptin.[7] This effect was maintained to week 52 in both trials. Ertugliflozin consistently reduced body weight in the VERTIS trials.[1-7]

Ertugliflozin added to usual therapy has also been investigated in people with stage 3 chronic kidney disease (estimated glomerular filtration rate of ≥30 to <60 mL/min/1.73 m^2) in the VERTIS RENAL trial.[8] However, after 26 weeks of treatment, ertugliflozin was not more effective at lowering HbA1c than placebo (see Table).

The most common adverse events with ertugliflozin in the trials included genital mycotic infections (9–12% of women, 4% of men), increased urination (2.5%), vulvovaginal pruritis (1%) and increased thirst (1%). As with other SGLT2 inhibitors, ertugliflozin can cause volume depletion, particularly in those with an eGFR of less than 60 mL/min/1.73 m^2. Monitoring volume status and electrolytes is recommended if there is a risk of fluid loss such as diarrhoea, heat stress or severe infection. Patients may become hypotensive with ertugliflozin.

Ketoacidosis has been reported with this drug so patients should be assessed for risk factors before starting treatment (e.g. low-carbohydrate diet, dehydration, acute illness, insulin dose reduction, alcohol misuse).

Ertugliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were greater in people with impaired renal function but were reversible when the drug was stopped. Renal function should therefore be monitored before and during ertugliflozin and when concomitant drugs that may affect renal function are used. Ertugliflozin is contraindicated in patients on dialysis, and in those with an eGFR of less than 30 mL/min/1.73 m^2 or persistently less than 45 mL/min/1.73 m^2.

Lower limb amputations were more common in people receiving the higher ertugliflozin dose (0.47% with 15 mg dose) than those who received the lower dose (0.06% with 5 mg dose) or the comparator (0.07%). Lower limb amputations have previously been found with canagliflozin which is no longer registered for use in Australia.

There have been no clinical studies of ertugliflozin in pregnancy or lactation. However in animal studies, the drug crossed the placenta and was excreted in the milk of lactating rats. At high doses, fetal

Table **Efficacy of ertugliflozin in clinical trials**

Study (duration, participants, mean baseline HbA1c)	Daily treatment	Trial outcomes*	
		Change in HbA1c	Body weight (kg)
Monotherapy			
VERTIS MONO[1] (26 weeks, 461 patients, baseline HbA1c 8.2%)	ertugliflozin 5 mg	−0.8%	−3.2
	ertugliflozin 15 mg	−1.0%	−3.6
	placebo*	+0.2%	−1.4
Initial combination therapy			
VERTIS SITA[3] (26 weeks, 291 patients, baseline HbA1c 8.9%)	ertugliflozin 5 mg + sitagliptin 100 mg	−1.6%	−2.9
	ertugliflozin 15 mg + sitagliptin 100 mg	−1.7%	−3.0
	placebo	−0.4%	−0.9
Add-on therapy to metformin ≥1500 mg			
VERTIS MET[4] (26 weeks, 621 patients, baseline HbA1c 8.1%)	ertugliflozin 5 mg	−0.7%	−3.0
	ertugliflozin 15 mg	−0.9%	−2.9
	placebo	0%	−1.3
Add-on therapy to metformin ≥1500 mg			
VERTIS SU[5] (52 weeks, 1326 patients, baseline HbA1c 7.8%)	ertugliflozin 5 mg	−0.6%	−3.0
	ertugliflozin 15 mg	−0.6%	−3.4
	glimepiride 6 or 8 mg	−0.7%	+0.9
Add-on combination therapy to metformin ≥1500 mg			
VERTIS FACTORIAL[6] (26 weeks, 1233 patients, baseline HbA1c 8.5–8.6%)	ertugliflozin 5 mg + sitagliptin 100 mg	−1.5%	−2.5
	ertugliflozin 15 mg + sitagliptin 100 mg	−1.5%	−2.9
	ertugliflozin 5 mg	−1.0%	−2.7
	ertugliflozin 15 mg	−1.1%	−3.7
	sitagliptin 100 mg	−1.1%	−0.7
Add-on therapy to metformin and sitagliptin ≥1500 mg			
VERTIS SITA2[7] (26 weeks, 464 patients, baseline HbA1c 8%)	ertugliflozin 5 mg	−0.8%	−3.4
	ertugliflozin 15 mg	−0.9%	−3.0
	placebo	−0.1%	−1.3
Add-on therapy in stage 3 chronic kidney disease†			
VERTIS RENAL[8] (26 weeks, 468 patients, baseline HbA1c 8.2%)	ertugliflozin 5 mg	−0.3%	−1.3
	ertugliflozin 15 mg	−0.4%	−1.4
	placebo	−0.3%	+0.5

HbA1c glycated haemoglobin

* least squares mean change from baseline

† Ertugliflozin was added to usual diabetes therapy (e.g. insulin and sulfonylureas), however metformin, rosiglitazone and other SGLT2 inhibitors were not allowed.

viability was reduced and cardiac malformations were increased. Ertugliflozin also affected kidney development when given to juvenile rats.

After once-daily oral administration, ertugliflozin is rapidly absorbed and steady state is reached within 4–6 days. Ertugliflozin is metabolised by UGT1A9- and UGT2B7-mediated O-glucuronidation. Its elimination half-life is 16.6 hours and it is excreted in the faeces (41%) and urine (50%). Drug–drug interactions are not expected with ertugliflozin. However, concomitant insulin or an insulin secretagogue can increase the risk of hypoglycaemia and lower insulin doses may be required.

Ertugliflozin has similar efficacy and safety in type 2 diabetes to other SGLT2 inhibitors, although comparative trials have not been carried out. In the VERTIS trials, it reduced HbA1c when used on its own or in combination with metformin and sitagliptin. Its efficacy is dependent on renal function, and people with moderate renal impairment did not benefit in the trials.

T T manufacturer provided additional useful information

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.

REFERENCES

1. Terra SG, Focht K, Davies M, Frias J, Derosa G, Darekar A, et al. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. Diabetes Obes Metab 2017;19:721-8. https://doi.org/10.1111/dom.12888
2. Aronson R, Frias J, Goldman A, Darekar A, Lauring B, Terra SG. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes Obes Metab 2018;20:1453-60. https://doi.org/10.1111/dom.13251
3. Miller S, Krumins T, Zhou H, Huyck S, Johnson J, Golm G, et al. Ertugliflozin and sitagliptin co-initiation in patients with type 2 diabetes: the VERTIS SITA randomized study. Diabetes Ther 2018;9:253-68. https://doi.org/10.1007/s13300-017-0358-0
4. Gallo S, Charbonnel B, Goldman A, Shi H, Huyck S, Darekar A, et al. Long-term efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: 104-week VERTIS MET trial. Diabetes Obes Metab 2019 Jan 7 [Epub ahead of print] https://doi.org/10.1111/dom.13631
5. Hollander P, Liu J, Hill J, Johnson J, Jiang ZW, Golm G, et al. Ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: the VERTIS SU randomized study. Diabetes Ther 2018;9:193-207. https://doi.org/10.1007/s13300-017-0354-4
6. Pratley RE, Eldor R, Raji A, Golm G, Huyck SB, Qiu Y, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. Diabetes Obes Metab 2018;20:1111-20. https://doi.org/10.1111/dom.13194
7. Dagogo-Jack S, Liu J, Eldor R, Amorin G, Johnson J, Hille D, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study. Diabetes Obes Metab 2018;20:530-40. https://doi.org/10.1111/dom.13116
8. Grunberger G, Camp S, Johnson J, Huyck S, Terra SG, Mancuso JP, et al. Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: the VERTIS RENAL randomized study. Diabetes Ther 2018;9:49-66. https://doi.org/10.1007/s13300-017-0337-5